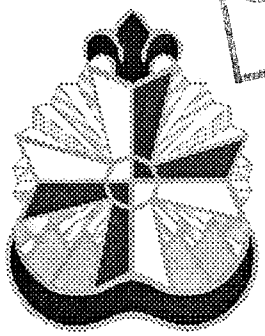
ANNUAL PROGRESS REPORT

FY 94



DEPARTMENT OF CLINICAL INVESTIGATION
WILLIAM BEAUMONT ARMY MEDICAL CENTER
EL PASO, TEXAS 72290-5001

CLINICAL INVESTIGATION PROGRAM
RCS MED-300 (R1)

HEADQUARTERS
WILLIAM BEAUMONT ARMY
MEDICAL CENTER
EL PASO, TEXAS 79920-5001

ANNUAL PROGRESS REPORT
FISCAL YEAR 1994

CLINICAL INVESTIGATION PROGRAM
RCS MED-300 (R1)

This report was prepared under the direction of
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Chief, Department of Clinical Investigation
William Beaumont Army Medical Center
El Paso, Texas 79920-5001

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1 JANUARY 1994	ANNUAL OCT 93 - SEP 94

4. TITLE AND SUBTITLE

Annual Research Progress Report FY94

5. FUNDING NUMBERS

6. AUTHOR(S)

COL IDELLE M. WEISMAN

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Department of Clinical Investigation
William Beaumont Army Medical Center
El Paso, TX 79920-5001

8. PERFORMING ORGANIZATION REPORT NUMBER

RCS-MED-300(R1)

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Office of the Surgeon General
Department of the Army
Washington, DC 20314

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

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13. ABSTRACT *(Maximum 200 words)*

Subject report identifiers the research activities conducted at William Beaumont Army Medical Center by investigators who had protocols approved by the Clinical Investigation Committee, the Institutional Review Board, and the Animal Use Committee. This report includes all protocols registered with the Department of Clinical Investigation during FY 1994. All known presentations and publications are also included. The research protocols described were conducted under the provisions of AR 40-38 (Clinical Investigation Program); AR 40-7 (Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Substances); AR 70-25 (Use of Volunteers as Subjects of Research); HSC 40-23 (Management of Clinical Investigation Protocols and Reports); and AR 70-18 (The Use of Animals in DoD Programs).

14. SUBJECT TERMS

clinical investigations; publications; presentations; detail summary sheets (study objective, technical approach, progress & status); investigator index; keyword index

15. NUMBER OF PAGES
208

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	

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FOREWORD

Fiscal year 1994 seems to be a corner that was turned by the Department of Clinical Investigation. In the spirit of the "Little Train That Could", our department continued further than our budget, manpower, and common sense would dictate. For many departments, losing an experienced Chief, as well as the Clinical Protocol Coordinator/ Editorial Assistant within one month of each other would dictate a season of conservatism, of pulling in, of trying to not lose turf. These are the obstacles that our department faced with the retirement of Colonel Manuel Schydlower, and the departure of Ms Vivian Maheu during the summer months. I was fortunate to be selected to guide the department in these difficult times. Rather than merely defend established turf, we chose to go out and conquer new turf. Central to our efforts was an afternoon long seminar in which the leadership of F.A.C.T., the Henry M. Jackson Foundation, and our own Major John Grabenstein from C.I.R.O. pounded into the minds of 52 WBAMC and El Paso physicians, nurses and administrators how to bring in money for TDY, supplies, CEEP and even MEDCASE buys by taking advantage of research funding possibilities. The effect was immediately felt, as we can boast of having arranged two CRDAs, worth almost $130,000. Also as a direct result of that meeting have been several generous gifts and donations, as well as several wonderful multicenter studies. We have seen the future, and in the age of shrinking federal dollars, our growth lies in a sea of alphabet soup spelling out things such as CRDA, PTNS, FACT and HMJF.

The future also contains the same extraordinary background that we have always had at WBAMC, including Dr. Veit's highly advanced tumor DNA analysis laboratory, Dr. Bhattacharyya's revolutionary work in respiratory tract mucin production and control, Major Nauschuetz's gene amplification laboratory, and my state of the art human performance laboratory. Major Richard Harris deserves kudos for establishing several surgery training programs which he does in our AAALAC-accredited facility along with physicians from El Paso civilian medical treatment facilities. But even more than the science, our future is built on a foundation of fierce commitment to the nurses, physicians and administrators who are our customers. The carpets in our department are becoming worn from the increase in customer traffic, and we, in turn spend less time in our labs, and more time in the other departments of this medical center, lecturing, guiding, and cajoling. We are growing.

It is not usual to grow in times of key manpower losses. We most probably could not have done it without the invaluable help of our student aide, Ms Tanya V. Marin. In an incredible act of selflessness, the Veterinary Clinic loaned us the capable services of Ms Liz Young for several months. We shall soon have a new Protocol Coordinator. And we will successfully continue into the future.

IDELLE M. WEISMAN, MD
COL, MC
Chief, Dept of Clinical Investigation

UNIT SUMMARY FY 94

OBJECTIVES

The Department of Clinical Investigation is responsible for providing the facilities and atmosphere of inquiry necessary to support and stimulate basic and clinical medical investigation within William Beaumont Army Medical Center.

TECHNICAL APPROACH

The Department of Clinical Investigation provides support for staff, fellows and housestaff research projects under the guidelines of the Clinical Investigation Program (AR 40-38); Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances (AR 40-7); Use of Volunteers as Subjects of Research (AR 70-25); Management of Clinical Investigation Protocols and Reports (HSC Reg 40-23); and The Use of Animals in DoD Programs (AR 70-18). Research protocols utilizing laboratory animals also adhere to the guidelines set forth in the "Guide for Laboratory Animal Facilities and Care" (published by the National Academy of Sciences-National Research Council) and the criteria established by the AAALAC.

Research is conducted under protocols approved by the WBAMC Clinical Investigation Committee, Human Use Committee, Radioisotope Committee, and Animal Use Committee, as applicable. Committee membership is governed by WBAMC Reg 15-1.

MANPOWER

Listed below is the strength of the Department of Clinical Investigation during FY 94.

Description	Grade	MOS	Br	Req	Auth	Name	Rank
C, DCI	O6	60F	MC	1	1	Weisman	O6
Biochemist	O3	68C	MS	1	1	Nauschuetz	O4
C, Bio Res Svc	O3	64C	VC	1	1	Harris	O4
Animal Care NCO	E6	91T	NC	2	1	Williams	E5
Animal Care Sp	E4	91T		1	1	Milbradt	E5
Animal Care Sp	E3	91T		2	1	Charles	E4
Supv Res Chem	12	1320	GS	1	1	Bhattacharyya	12
Microbiologist	12	403	GS	1	1	Veit	12
Chemist	09	1320	GS	1	1	Enriquez	09
Microbiologist	09	403	GS	1	1	Smiley	09
Med Tech	07	645	GS	2	1	Lund	07
Med Tech	07	645	GS	2	1	Manna	07
Med Tech	07	645	GS	2	1	McIntyre	07
Health Tech	07	640	GS	1	1	Revels	07
Cl Prot Specialist	09	301	GS	1	1	Vacant	
Sup Clk	05	2005	GS	1	1	Turner	05
Anim Caretaker	04	5048	WG	1	1	Sigholz	04
Anim Caretaker	01	5048	WG	2	1	Burton	01

Civilian Personnel with Special Project Funding and Temporary Civilians

	Grade	Series		Name
Co-Director HP/SCT				Zeballos
Exercise Physiologist	09	413	GS	Taylor
Exercise Physiologist				Connery
Student Hire	01	3506	YW	Marin

PERSONNEL

	Req	Auth.	Actual
Officers	3	3	3
Enlisted	5	3	3
Civilian	16	11	15*

*4 civilians are funded through grants and 1 part-time student hire.

Changes in personnel during FY 94:

COL Schylower retired in Jul 94; duties assumed by COL Weisman
Ms. Vivian Maheu left the El Paso area
Mr. Sean Connery was hired in support of a grant

GRANTS

USA Medical Research and Development Command

Comparison of Cranial and Iliac Autologous Bone Grafts and Their Effect on the Success Rates of Subsequent Osseointegrated Intra/Extraoral Implant Application in the Miniature Swine. $2,000

Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model. $4,000

Effect of Fibrin Sealant on Skin Graft Inhibition of Wound Contraction in the Porcine Model $1,000

Effect of Fibrin Sealant on Breaking Strength of Incisional Wounds in the Porcine Model $2,390

Impact of Smoking on Aerboic and Anaerobic Performance Driving Upper and Lower Body Exercies in Female Soldiers. (Defense Women's Health Research Program) Log W4166009 $150,000

Effect of Atrovent (Ipratopium Bromide) Inhalation Aerosol on Exercise Performance in Patients with Chronic Pulmonary Obstruct Pulmonary Disease $70,000 (Boehringer Ingleheim, Ltd.)

Acute Airway Injury and Response: Combined Effect of Smoke Inhalation and Combustion Products on Mucin Gene Expression and Regulated Mucin Production in the Tracheal-bronchial Epithelium $48,000

Cooperative Research and Development Agreements (CRDAs)

MAJ Bruce Pichoff, Dept of Pediatrics (PI), with MedImmune, Inc Gaithersburg, MD (Provider) and PPD, Wilmington, NC (Intermediary) "A Phase III Randomized, Double-Blind, Placebo-Controlled Trial of RespiGam™ (RSVIG-IV) Infusions for Reduction of the Rate of RSV Hospitalization in Premature Infants and Infants with Bronchopulmonary Dysplasia" Total worth approximately $122,000. Amount received to date: $29,520

MAJ Bill Nauschuetz, Dept of Clinical Investigation (PI), with BioVenture, Inc., Murfreesboro, TN. "Amplification of *Mycobacterium tuberculosis* to Predict Antimicrobial Resistance Using a Novel Single-Step DNA Extraction, Polymerase Chain Reaction and Gene Sequencing" Total worth $5,400. Amount received to date: $0.00 (awaiting final approval).

PROTOCOLS, PRESENTATIONS, PUBLICATIONS

Protocols	Ongoing	New	Completed	Terminated
FY 92	114	67	39	26
FY 93	110	54	29	30
FY 94	91	44	28	31

	Publications	Presentations
FY 92	40	57
FY 93	32	78
FY 94	47	76

EXPENDITURES

	FY 92	FY 93	FY94
Personnel (Civilian)	533,655	520,798	510,723
Consumable Supplies	229,484	258,409	152,517
Capital Equipment	131,810	15,007	9,313
TDY	10,762	8,127	3,966
Printing and Publications	2,494	1,760	1,066
Total	**908,205**	**804,101**	**677,585**
MEDCASE Equipment	164,964	0	64,532
Military Pay	543,248	559,043	491,485
TOTAL	**1,616,415**	**1,363,144**	**1,239,602**

PROGRESS FY 94

Biological Research Service

The William Beaumont Biological Research Service laboratory animal facility has been fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1968. Currently, this facility, totaling 7,134 square feet, occupies three buildings on the William Beaumont Army Medical Center (WBAMC) complex. The main facility, in Building 7776, contains the surgical suites, radiology, treatment rooms, necropsy, the majority of the animal holding areas, and the administrative offices. Building 7774, is utilized as a large equipment storage area, plus a 250 square foot, Class 10,000 bioclean room that became operational last year. The third unit is a 150 square foot, walk-in refrigerator that provides excellent long term storage of rations required by the research animals.

As was true for the past several years, the Biological Research Service has been extremely active in its support of training, research, and collaborative protocols in FY94. Of the presently 33 active protocols, 14 training protocols were supported in FY94 for medical personnel encompassing emergency trauma life support, general surgery, laser surgery, laparoscopic techniques, and vascular microsurgery. Of particular note was the exceptional support provided to the Pediatric Advanced Life Support (PALS) Course, accredited by the American Heart Association and the Advanced Trauma Life Support (ATLS) Course accredited by the American College of Surgeons.

The 19 research protocols supported by the Biological Research Service were not only practical and militarily relevant, but continued to expand recently established areas of research heretofore lacking at WBAMC. Research continued in the disciplines of microsurgery, soft tissue and orthopedic reconstruction materials and techniques, surgical laser applications, laparoscopic and thoracoscopic methodologies, therapeutic efficacy, molecular biology, and immunology. The Biological Research Service realized over a 300% expansion of its recently established immunodeficient rodent colony and is moving aggressively into oncology, and particularly breast cancer research, dependent upon xenografts and propagation of foreign organisms.

WBAMC and the Biological Research Service have continued collaboration with the Sierra Medical Center in certification of physicians in the application of the surgical laser, as well expanding training protocols for the combat medical units of Fort Bliss.

The Biological Research Service received official notification in November 1993 that the laboratory animal care and use program continued to be fully accredited by AAALAC and no deficiencies were noted. The next on-site re-accreditation inspection by AAALAC will occur in 1996 - the Biological Research Service will be ready.

Chemistry Section

The chemistry section of DCI is engaged in research projects concerning retinoic acid regulated differentiation and mucin gene expression of rat and rabbit tracheal epithelial cells in culture exposed to different toxic substances and respiratory drugs, analysis of hemoglobin peptides from humans and animals by high pressure liquid chromatography and capillary electrophoresis, and analysis of drug metabolites in children of addicted parents.

We have demonstrated that retinoic acid (vitamin A), both all-trans and 13-cis, is one of the most important constituents of the culture medium in which tracheal epithelial cells differentiate and propagate normally. Without retinoic acid, the cells tend not to grow properly, nor do they produce mucin, the secretion of which is the normal function of these cell lines. Ultrastructural examination of the tracheal cells grown in medium containing retinoic acid shows well-established mucociliary epithelium with abundant microvilli and secretory granules. On the other hand, when the cells are grown in medium without retinoic acid, the cells tend to become squamous and lose most microvilli and secretory granules. Hybridization analysis of total RNA isolated from cells grown in medium with retinoic acid indicates the strong expression of mucin gene. The expression becomes weaker in cells grown without the compound. Addition of retinoic acid to the cells grown in medium without retinoic acid results in full expression of mucin gene. Additionally, we have found that retinoic has a protective action against many toxic substances which were injurious to these cell lines. We have also found that mucin antisense oligomer has an inhibitory effect on retinoic acid-induced mucin gene expression and secretion in tracheal epithelial cell lines. These findings have important implications regarding respiratory diseases such as asthma, chronic bronchitis and cystic fibrosis, where excessive secretion of mucous is a common phenomenon. We are also now involved in a protocol,
funded by USAMRD, concerning effect of retinoic acid and antisense oligomer on mucin gene expression and injury to the tracheal epithelium exposed to smoke. We have found that mucin gene expression is increased considerably in epithelium exposed to smoke. We are now engaged in doing experiments on the effect of antisense oligomer on mucin gene expression in thin cell lines.

We are also involved with two other protocols, entitled," The effect of bovine TSH on hemoglobin proportions in adult rats," and "Determination of the prevalence of drug affected babies in a military population." The first was prompted by observations that in patients with beta globin chain hemoglobin abnormalities, a high level of fetal hemoglobin is associated with a milder clinical course and that during the postnatal period in humans, there is a switch from fetal hemoglobin (HgbF) to adult hemoglobin (HgbA). A model system has been developed to study the level of hemoglobin components in adult and neonate rats. However, estimation of HgbF level by classical procedures was slow and tedious. We have developed a rapid and sensitive procedure which utilizes high pressure liquid chromatography with a weak cation exchange column and capillary electrophoresis to characterize and compare adult and neonate rat hemoglobin components more effectively.

The last ongoing protocol is concerned with determination of drug metabolites in mecqnium of babies that may have been acquired from mothers before delivery. We are now analyzing drug metabolites in meconium by employing gas chromatography/mass spectrometry methods.

Molecular Biology Service

The Infectious Disease Research Laboratory (IDRL), Department of Clinical Investigation performs clinical gene amplifications. The laboratory is staffed by one 0-4 and one GS-07 Medical Laboratory Technician. Current protocols include the polymerase chain reaction (PCR) to DETECT *Mycobacterium tubersulosis.* in a variety of clinical specimens, including sputum and spinal fluid. The section is also using PCR-SSCP (single-strand conformation polymorphism) to detect rifampin and isoniazid resistance in *M. tuberculosis.* The section is working with several El Paso area hospitals, as well as the El Paso Citry/County Health District to collect specimens.

We are currently establishing a satellite PCR laboratory for the use of the Microbiology Section, Department of Pathology and the Department of OB/GYN. This laboratory will primarily do amplifications to detect human papillomavirus (HPV) in gneital specimens, as well as colostrum and other body fluids. The section has also collected genital specimens from adolescent males and females specimens in order to do *in situ* PCR amplification for E6 and E7 mRNA. The section has also done PCR on dialysates to detect hepatitis C virus (HCV).

The equipment used by the IDRL in these protocols includes the Bactec 460 with TB Hood, Perkin Elmer Model 392 DNA Synthesizer, the Perkin Elmer 9600 thermal cycler, and the Perkin Elmer QPCR 5000. DCI is purchasing a Perkin-Elmer 2400 for the OB/GYN-Pathology satellite PCR laboratory.

Immunology and Microbiology Section

Research interests of the Immunology and Microbiology Section are focused primarily on in vitro and in vivo studies of growth regulatory factors such as estrogen, epidermal growth factor, transforming growth factors, and insulin-like growth factors which influence the growth of human breast cancer cells and on studies of breast cancer cell apoptosis (programmed cell death)

Our studies of human breast cancer cells are directed toward understanding the regulatory influences that autocrine and paracrine-mediated growth factors exert during the growth cycle of breast cancer cells. Breast tumors with high S-phase fractions (more rapidly growing tumors) have high rates of metastasis and poor prognoses even though the largest tumor cell kill attained with chemotherapeutic agents is in tumors with high S-phase fractions. An alternative approach to conventional cancer chemotherapy (which attempts to inhibit DNA synthesis during the S-phase of the cell cycle) is to prevent rapidly cycling cells from proceeding through the growth phases of cell cycle.

Both normal and malignant breast epithelial cells are dependent on paracrine and/or autocrine growth
stimulation to induce their movement through cell cycle (mitogenesis). Without appropriate mitogenic signals, quiescent tumor cells remain in G_0/G_1 until they either become activated to proceed through the cell cycle or are terminated through one of two processes: (1) necrosis or, (2) apoptosis (programmed cell death). Apoptosis is not a random event. It appears to be initiated by a signal (i.e. absence of growth factor) which triggers an increase in intra-cellular free Ca^{++} which, in turn, activates a Ca^{++}/Mg^{++}-dependent endonuclease which carries out the orderly degradation of the cell's DNA. Failure of a tumor cell to receive the appropriate cell cycle progression stimuli constitutes a decision point for that cell. Rather than passively awaiting appropriate mitogenic signals in G_0/G_1 indefinitely, quiescent tumor cells recognize the absence of growth factor stimuli and proceed with the initiation of auto-degradation or apoptosis. Growth factor deprivation may provide an alternative approach to therapeutic elimination of tumor cells. Treatment modalities which bring about a suppression or modification of growth factor production and/or secretion and/or receptor binding by either stromal cells (paracrine stimulation) or by tumor cells themselves (autocrine stimulation) may be provide an effective alternate approach to breast cancer therapy.

Agents such as camptothecin, glucocorticoids, tumor necrosis factor, transforming growth factor, lymphotoxin, irradiation, hyperthermia, and actinomycin D have been shown to induce apoptosis in a variety of different cell lineages, both normal and malignant. We have utilized an in situ digoxigenenin-nucleotide labeling technique to detect apoptosis in two human breast cancer cell lines, DU4475 and BT-474. DNA fragmentation that occurs in apoptotic cells results in the generation of many new free 3'-OH DNA ends. By contrast, normal or proliferating cells have very few (non-detectable) DNA fragments with free 3'-OH ends. The new 3'-OH ends produced as the result of the apoptotic process represent a useful labeling target to attach residues of digoxigenin-nucleotide via terminal deoxynucleotidyl transferase. The added nucleotides are detected with peroxidase-labeled anti-digoxigenin antibodies and a chromogenic substrate. Correlation of apoptosis induction and cell cycle progression is determined by flow cytometric and digital image analyses.

It is hoped that our studies will provide a better understanding of the relationship between growth factor deprivation and the initiation of apoptosis. Therapeutic approaches which facilitate growth factor deprivation and, hence, induce apoptosis, may provide an effective alternate method of tumor destruction.

Human Performance Laboratory

The Human Performance Laboratory at William Beaumont Army Medical Center is a full service cardiopulmonary exercise testing laboratory with multiple research and clinical exercise testing capabilities. As a major regional tertiary referral hospital (300 bed) WBAMC serves a large retired, active duty military and dependent population. The Human

Performance Lab is responsible for all asthma exercise protocols as well as cardiopulmonary exercise testing for the medical center and its regional responsibilities.

The Human Performance Laboratory's personnel include an active duty military M.D., an M.D., Ph.D. (civilian), and a GS-9, DAC exercise physiologist. The laboratory is contiguous to a state of the art pulmonary function laboratory which includes: two body plethysmographs, two pulmonary function systems with nitrogen washout for lung volume and D_LCO determinations, bronchial provocation capability, and arterial blood gas machines.

A large clinical and extremely large volunteer population at Fort Bliss make research projects with large n values feasible.

A comprehensive listing of the laboratory's capabilities include: state of the art cardiopulmonary exercise testing which consists of ability to measure metabolic (VO_2, VCO_2, Anaerobic threshold, R), Ventilatory (VE, VT, F), Cardiovascular (ECG, HR, HR/VO_2, VO_2/work rate) and gas exchange (PaO_2, $P(A\text{-}a)O_2$, SaO_2, VD/VT, pH, $P(a\text{-}ET)CO_2$) parameters; simulation of different environmental conditions utilizing FIO_2 manipulation (inspiratory hypoxia simulating, 2300 m, 4000 m, etc.); study of O_2 transport including O_2 dissociation curve (P_{50} capability and separate tonometry set-up); treadmill, cycle ergometry and arm crank modalities; reactive airways dysfunction - diagnostic - exercise induced bronchoconstriction, broncho-provocation, isocapnic hyperventilation, cold air (-10° C) hyperventilation decrease; vocal cord dysfunction - exercise induced, inhalational challenge, bronchoscopy with flow volume loop set-up for documentation; mechanics of breathing including P_{DI} determined (esophageal balloons) and pressure-volume (compliance) curve relationships; sub-maximal exercise D_LCO and measurement of pulmonary capillary blood volume (developing); non-invasive determination of cardiac output using CO_2 rebreathing technique and acetylene during intrabreath technique; invasive determination of pulmonary gas exchange: SaO_2, PaO_2, $P(A\text{-}a)O_2$, VD/VT, $P(a\text{-}ET)CO_2$; monitoring: weight - sauter scale (accuracy 10 gm), temperature - esophageal, rectal, skin probes (sensor tech system), SpO_2 - HP and pulse oximeters, BP - direct BP monitoring; lactate determination capability; capability ofV_{O_2}, V_{CO_2}, andV_E determination under field conditions using dry gas meter and Douglas bag collection; state of the art in house nuclear cardiology and cardiovascular laboratories provide in house research/clinical interaction on issues related to human performance.

The Human Performance Lab has in the past gained national recognition for its work in Sickle Cell Trait. Presently, it is a force in standardization of clinical exercise testing. As such, it serves as a major reference laboratory.

The Human Performance Lab has received extramural funding though the Jackson Foundation for research in COPD; additional extramural funding opportunities are presently being considered.

PUBLICATIONS

Department of Clinical Investigation

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Department of Nursing

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PRESENTATIONS

Department of Clinical Investigation

Bhattacharyya SN, Manna B: Tracheal Epithelial Cell Injury and Mucin Gene Expression: Effect of Retinoids. Annual Meeting of Society of Armed Forces Medical Laboratory Scientists. Reno, NV 13-17 Mar 94.

Bhattacharyya SN: Retinoic Acid Regulated Mucin Gene Expression in Tracheal Epithelial Cells. Presented to Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics. Calcutta, India, 31 May 94.

Enriquez JI, White EL, Pearson JT, Critz W: The Analysis of Rat Hemoglobin Components: A Comparison Between HPLC and Capillary Electrophoresis. 4th Annual Meeting of the American Association for Clinical Chemistry. New Orleans, LA, July 18-21, 1994.

Nauschuetz W, Harrison L: Still a Catchy Subject. Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists. Reno, Nevada, March 1994.

Nauschuetz W: The Clinical Gene Amplification Laboratory. Seventh Medical Command Army Medical Department/Military Service Cops Conference. Garmisch, Germany, April 1994

Nauschuetz W, Mahon C: Clinical Microbiology Review. American Society of Clinical Pathologists. Chicago, Illinois, May 1994.

Nauschuetz W: Update on Bacterial Vaginosis. Texas Teleconference Network. 24 May 1994.

Nauschuetz W, Greenberg H, Dudrey E, Johnson D, Tinkle M, Amaya M: Sensitivity of pap smear, Virapap and colposcopy in the detection of human popillomavirus infection in Hispanic women. Annual Meeting of the Western Association of Gynecologic Oncologist and Gynecologic Oncologist of Canada. Whistler, British Columbia. June 1994.

Nauschuetz W, Whiddon R: Clinical Gene Amplification. Texas Teleconference Network. 13 September 1994.

Schydlower M: Lecture. Dept of Pediatrics, University of California at San Diego School of Medicine. San Diego, CA, 18 Oct 93.

Schydlower M: Grand Rounds. Department of Pediatrics, Texas Tech School of Medicine. Lubbock, TX, 19 Nov 93.

Schydlower M, Stafford L, Imai W, Brantner L: Adolescent Health Screening: Risky Business. Workshop. 28th Annual Uniformed Services Pediatric Seminar, American Academy of Pediatrics. Seattle, WA, 13-17 Mar 94.

Smiley B, Veit BC: Proliferative Activity of Suppressor Cells in Bermuda Grass Allergy. Annual Meeting of Military

Medical Laboratory Science. Reno, NV, 13-17 Mar 94.

Weisman IM: Cardiopulmonary Gas Exchange Effects of Stressful Exercise at Altitude in SCT and Controls. 1993 Annual Meeting of the American College of Chest Physicians. Orlando, FL, 24-28 Oct 93.

Weisman IM, Zeballos RJ: Interdisciplinary Approach to Cardiopulmonary Exercise Testing. American College of Chest Physicians meeting. Orlando, FL, 26 October 1993.

Weisman IM, Zeballos RJ: Interdisciplinary Approach to Cardiopulmonary Exercise Testing. Clinical Applications of Exercise Testing. Orlando, FL, 28 October 1993.

Weisman IM: Preoperative Evaluation for Lung Resection. Long Island Pulmonary Society. Westbury, LI, 29 November 1993.

Weisman IM: Clinical Exercise Testing; Coccidioidomycosis. Winthrop University. Mineola, N.Y., 29-30 November 1993.

Weisman IM: Issues in Exercise Testing. Pulmonary Grand Rounds - Sam Jaffe Memorial Lecture. Mount Sinai School of Medicine, New York City, 15 April 1994.

Weisman IM: Interpretation of Heart Rate and Cardiac Variables. 1994 American Thoracic Society Meeting post-graduate course entitled "Performance and Interpretation of Clinical Exercise Testing." 21 May 1994.

Weisman IM: Clinical Topics in Pulmonary Medicine. Clinical Exercise Rounds. 25 May 1994.

Weisman IM: Pulmonary Function Testing and Exercise Testing. Tenth National American College of Chest Physicians Board Review Course. Los Angeles, CA, 3-7 June 1994.

Zeballos RJ: The Need for Standardization of Cardiopulmonary Exercise Testing. Regional ACP meeting. Orlando, FL, 4-8 Nov 93.

Zeballos RJ: Clinical Exercise Testing, Exercise Induced Asthma. American Thoracic Society Post Graduate Course. Boston, MA, 21 May 94.

DENTAC

Dickerson N: Pre-Prosthetic Surgery. 10th International Congress of the Academy of Dental Specialist. Ciudad Juarez, Chihuahua Mexico, Oct 93.

Dickerson N: Autologous Calvarial and Iliac Onlay Grafts with Immediate Implant Placement. Southwest Society of Oral and Maxillofacial Surgeons Annual Meeting. San Antonia, Texas, Apr 94.

Dickerson N: Expanded Polytetrafluoroethylen (e-PTFE) for Reconstruction of Orbital Floor Fractures. Southwest Society of Oral and Maxillofacial Surgeons Annual Meeting. San Antonio, Texas, Apr 94.

Donovan M: 44th Annual Postgraduate Short Course in Oral and Maxillofacial Surgery. Walter Reed Army Medical Center, Oct 93.

Donovan M: Maxillary and Madibular Reconstruction with Calvarial Bone Grafts and Branemark Implants. 6th International Dental Congress. Cairo, Egypt, Nov 93.
Donovan M: Maxillary and Mandibular Reconstruction with Calvarial Bone Grafts and Branemark Implants. Alexandria, Egypt, Nov 93.

Donovan M: Airway Adjuncts. ACLS Course, William Beaumont Army Medical Center. Jan 94.

Donovan M: Update and Research on Bone Grafting Techniques. Louisiana State University School of Medicine in Shreveport. Mar 94.

Donovan M: Implantology for the General Dentist. 30th Annual Allyn D. Burke Dental Symposium. Monterey, California, May 94.

Mitchell J: Complication Exodontia. 10 International Congress of the Academy of Dental Specialist. Ciudad Juarez, Chihuahua Mexico, Oct 93.

Mitchell J: Otrhognathic Surgery. Fort Knox, Kentucky, May 94.

Mitchell J: Maxillofacial Trauma. Fort Knox, Kentucky, May 94.

Mitchell J: Dental Implants. Fort Knox, Kentucky, May 94

Mitchell J: TMJ Surgery. Fort Knox, Kentucky, May 94.

Department of Medicine

Jimenez C, Cannady PB, Omori DM, Berry, DS: Evaluation of the Night Float System. Army 10th Annual Scientific Meeting of American College of Physicians. Orlando, FL, 18-19 Nov 93.
Gormely, Thomas S: Testicular Microlighiasis: 1994 South Center Section of the American Urological Association, Inc. Aug 94.

Keenan LM: Do Not Resuscitate: Do Not Provide Care? 59th Annual International Scientific Assembly of American College of Chest Physicians. Orlando, FL, 24-28 Oct 93.

Keenan LM, Willadsen DS, Roth BJ: Malignant Fibrous Tumor of the Pleura with Unusual Metastasis. 59th Annual International Scientific Assembly of American College of Chest Physicians. Orlando, FL, 24-28 Oct 93.

Maldonado ME: Oxygen Saturation After Colonoscopy. 1993 US Army American College of Physicians Meeting. Orlando, FL 17-21 Nov 93.

Morse R, Belbel R: Pre-Operative Evaluation Compared to Patient Outcomes: An Army Medical Center Experience for Vascular Surgery. Army 10th Annual Scientific Meeting of American College of Physicians. Orlando, FL, 18-19 Nov 93.

Pacheco E: Effect of Meal Consumption on Radionuclide Ventriculography. 39th Annual Meeting of the Southwestern Chapter of the Society of Nuclear Medicine. Albuquerque, NM, 7-10 Apr 94.

Simcic KJ: Severe Refractory Paget's Disease of Bone Responsive to a Single Intravenous Dose of Pamidronate. 1993 US Army American College of

Physicians Meeting. Orlando, FL, 17-21 Nov 93.

Szyjkowski R: Impact of Helicobacter pylori on Acute Inflammation, Chronic Inflammation and Dysplasia in Barrett's Epithelium. 10th Army Regional Meeting of the American College of Physicians. Nov 93.

Department of OB/GYN

Brittain PC, Partial Hydatidiform Molar Pregnancy Presenting with Severe Preeclampsia Prior to Twenty Weeks Gestation. 1993 Annual Meeting of the Armed Forces District of the American College of Obstetricians and Gynecologists. Seattle, WA, 30 Oct - 4 Nov 93.

Brittain PC: Mitotically Active Uterine Leiomyoma. 1993 Annual Meeting of the Armed Forces District of the American College of Obstetricians and Gynecologists. Seattle, WA, 30 Oct - 4 Nov 93.

Bush M: Comparison of Azithromycin and Erythromycin in the Treatment of Cervical Chlamydial Infection During Pregnancy. 1993 Annual Meeting of the Armed Forces District of the American College of Obstetricians and Gynecologists. Seattle, WA, 30 Oct - 4 Nov 93.

Bush M: Comparison of Azithromycin and Erythromycin in the Treatment of Cervical Chlamydial Infection During Pregnancy. Presented to Dept of Ob/Gyn, Georgetown University Medical Center, 15 Jul 94

Maxwell GL: Tissue Glue as an Adjunct to Wound Healing in the Porcine Model 1993 Annual Meeting of the Armed Forces District of the American College of Obstetricians and Gynecologists. Seattle, WA, 30 Oct - 4 Nov 93.

Webb J: Vaginal Operative Delivery in Modern Obstetrics. 1993 Annual Meeting of the Armed Forces District of the American College of Obstetricians and Gynecologists. Seattle, WA, 30 Oct - 4 Nov 93.

Department of Pediatrics

Raszka, WV: Delayed Typed Hypersensitivity Skin Testing Children with Perinatally Acquired HIV Disease. 1994 Southern Section Meeting of the Society for Pediatric Research. New Orleans, LA, 3-5 Feb 94.

Raszka WV: Delayed Type Hypersensitivity (DTH) Skin Testing in HIV Infected (HIV+) Children. American Pediatric Society/Society for Pediatric Research meeting. Seattle, WA, 1-5 May 94.

Raszka WV, Moriarty RA, Ascher DP, Waeker NJ, Cieslak TD, Robb ML: Delayed Type Hypersensitivity Skin Testing in HIV-1 Infected (HIV+) Children. Uniformed Services Pediatric Seminar. Mar 94.

Raszka WV, Moriarty RA, Ascher DP, Waecker NJ, Ottolini MG, Goldberg DI, Krober MS, Robb ML: Stability and Prognostic Value of Serial Absolute and Percent CD4+ Lymphocyte Cell Counts in HIV-1 Infected (HIV+) Infants and Children. Uniformed Services Pediatric Seminar. Mar 94.

Waecker NJ, Ascher DP, Meyer GA, Raszka WV, Moriarty RA, Cieslak TJ, Ottolini MA, Krober MS, Goldberg DI, Robb ML, Military Pediatric HIV Consortium of the MMCARR: Age-Pediatrics Raszka WV, Skillman LP, McEvoy PL, Robb ML: Comparison of Non-Tuberculous Mycobacterial (NTM) Cultures from HIV-1 Infected (HIV+) and Uninfected (HIV-) Patients. Uniformed Services Pediatric Seminar. Mar 94.

Department of Psychiatry

Cottrell RW: From Clozapine to Resperidone. Army Psychiatry Conference. San Antonio, Texas (awarded as best paper by a military psychiatry resident), 30 Mar 94.

Cottrell RW: From Clozapine to Resperidone. Grand Rounds, Department of Psychiatry, Tripler Army Medical Center. Hawaii, 26 May 94.

Cottrell RW: From Clozapine to Resperidone. Department Conference, Honolulu Veterans Administration Mental Health Clinic. Honolulu, Hawaii, 8 Jun 94.

Scott CL: Managing the Borderline Personality Disorder. Department of Psychiatry, 67th CSH. Germany, Oct 93.

Scott CL: Interviewing the Psychiatric Patient. Wuerzburg University School of Medicine. Germany, Jan 94.

Scott CL: Tourette's Disorder. Military Psychiatry Conference. San Antonio, California, Mar 94.

Scott CL: Emergency Psychiatric Evaluations. European Medical School Conference. Germany, Apr 94.

Scott CL: Tourette's Disorder and CO Morbid Psychiatric Conditions. Grand Rounds, 67th CSH. Germany, May 94.

Regionalization & Managed Care

Pearl KK: Efficacy of Immunization with a Combination of Serum and Recombinant Hepatitis B Vaccines. 1994 Texas Public Health Association 69th Annual Convention. Corpus Christi, TX, 27 Feb - 2 Mar 94.

Department of Surgery

Choren A, O'Donnel S: Result of a Selective Approach for Varicose Vein Surgery. Gary P. Wratten Symposium, Mar 94.

Flynn TW: Comparison of Mechanical Power and Muscle Activity During Forward and Backward Walking. American Physical Therapy Association's Combined Sections Meeting. New Orleans, LA, 2-6 Feb 94.

Gormley TS: Testicula Microlithiasis. 1994 South Center Section of the American Urological Association, Inc. Aug 94.

Haberlin J, O'Donnell S, Hetz, S: Superior Vena Cava Filter Placement: A Case Report and Literature Review. Gary P. Wratten Symposium. Mar 94.

Kroll J, Morey A, Dresner M: Serum PSA Concentration: Defining a Normal

Rate of Change. 1993 AUA Western Section Annual Meeting. Nov 93.

Morey A, Deshon GE, Dresner M: Clostriduim Difficile Gastroenteritis as Postoperative Complication of Ileal Neobladder: Report of Two Cases and Review of Predisposing Features. 1993 Kimbrough Urological Seminar. Oct 93.

Morey A, Deshon GE, Dresner M: Clostriduim Difficile Gastroenteritis as Postoperative Complication of Ileal Neobladder: Report of Two Cases and Review of Predisposing Features. 1993 AUA Western Section Annual Meeting. Oct 93.

O'Donnell S: Assessment of Non-Invasive Evaluation of the Carotid Arteries Prior to Carotid Endarterectomy. Military Vascular Conference, Dec 93.

Shriver J, O'Donnell S: Angioscopic Venous Valvulotomy for Infraingunial Bypass. Gary P. Wratten Symposium, Mar 94.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/17 STATUS: Ongoing

TITLE: Human Tracheal Mucin: Biochemical, Physical and Rheological Studies

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 86 ESTIMATED COMPLETION DATE: Sep 95

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Manna, JI Enriquez

KEY WORDS: Tracheal Mucin, Human

Study Objective: This protocol is concerned with isolation, purification and characterization of mucin glycoprotein components (mucins) from tracheal secretion of patients with asthma, chronic bronchitis and cystic fibrosis. The glycosylated and nonglycosylated peptides will be isolated, purified and sequenced (peptide portion) after subjecting the purified mucins with different proteolytic enzymes. Antibodies will be developed in rabbits against the nonglycosylated peptides which, in turn, will be used to follow the synthesis and secretion of these macromolecules in a tracheal (or bronchial) culture system. Finally, the viscoelastic properties of purified mucins will be investigated.

Technical Approach:

1. Collect sputum from patients (either male or female, any age) with asthma, chronic bronchitis and cystic fibrosis.
2. Solubilize mucins with water and buffer.
3. Establish the homogeneity of mucin glycoproteins isolated from sputum of patients with asthma, chronic bronchitis, and cystic fibrosis by molecular sieve and ion-exchange chromatography.
4. Isolation and characterization of peptides (or glycopeptides) derived from digestion of mucins with different proteolytic enzymes (Column and HPLC);
5. Amino acid sequence analysis of these peptides by sequenator and DNA cloning procedure;
6. Raise antibodies in rabbits against these peptides (preferably against nonglycosylated peptides); and finally,
7. Establish a tracheal (or bronchial) culture system to examine the synthesis and control in secretion of these macromolecules by ELISA or radioimmunoassay (RIA) procedures using these antibodies.

In addition to the above, the physical properties of mucins, particularly their interaction (in terms of viscosity) with other serum proteins (such as albumin, immunoglobulin, and fibronectin) will be studied.

Progress: By utilizing the mucin antibody raised in rabbit against human mucin apoprotein, our laboratory, in collaboration with Dr. Kaufman and Dr. Batra of Duke University Medical Center, Durham, North Carolina, has been able to obtain several clones, few of which have already been sequenced. However, no report units, such as those found in other mucins, were noticed. The nucleotide sequence of one of the other remaining clones has just been completed and the sequence resembles a typical sequence profile of mucin. This clone was found to be expressed in a bronchocarcinoma cell line. The estimated completion date has changed from Oct 94 to Sep 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/16A STATUS: Ongoing

TITLE: Cellular Mechanism of Mucin Secretion: Studies Involving Rat and Rabbit Tracheal Culture System

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 89 ESTIMATED COMPLETION DATE: Sep 95

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Manna, JI Enriquez

KEY WORDS: Mucin, Animal

Study Objective: This proposal is concerned with the isolation and characterization of mucin glycoprotein components (mucin) from secretions of rat and rabbit tracheal epithelial cells in culture and establishing their structural identity with those of th

Technical Approach: Growth of epithelial cells from rat and rabbit bronchial tissues: Rats and rabbits will be euthanized and normal appearing tracheal tissues excised aseptically, immersed in cold, sterile L-15 culture medium containing penicillin\streptomycin and transported on ice to the laboratory. Lung tissue is sterilely trimmed away and the bronchus cut into large fragments. Cells are isolated from the human bronchus after an overnight incubation with 0.1% protease solution in minimal essential medium (MEM, Ca++free) done at 4 degrees C. The next day, incubated bronchi are flushed with MEM plus 10% Fetal Calf Serum to remove the digested cells. The cells are washed several times to remove any protease, which is toxic to epithelial cultures. The cell suspension is filtered through a sterile 100U nitrex filter and centrifuged for 10 minutes. Cell pellets are resuspended in cold MEM with 10% FCS and centrifuged again. The cold protease overnight treatment is sufficient to remove most epithelial cells lining the bronchus without much contamination of other cell types from the layer under the basement membrane. After the total cell count is taken, primary cultures are normally initiated by plating 1-2x 10 6 cells per ml per 35mm culture dish. The culture conditions used for the human bronchial epithelial cells consist of M199 media with D-valine substituted for Dl-valine, 10% Fetal Calf Serum, L-glutamine, penicillin/streptomycin, gentamicin, insulin, transferrin, epidermal growth factor, hydrocortisone, cholera toxin, bovine hypothalamus extract, and fungizone. Primary epithelial cultures were then placed in an incubator, with conditions of 37 degrees C., 5% C, and 95% air, and cells allowed to adhere to the culture dish. After 3-4 days incubation, a confluent primary culture of epithelial cells is routinely observed. The cultures received media change and can be used in various studies.

Secretion of mucin and characterization: The synthesis of mucin will be followed by 3H glucosamine and 35SO4 incorporation. Once the saturation curve is established, radioactive agents will not be used anymore. At the time of maximum secretion, the culture medium will be collected, lyophilized and chromatographed on Sepharose 2B and ECTEOLA column. The purified mucin will be deglycosylated by chemical procedure and the peptide portion will be partially sequenced by sequenator.

Isolation of mucin mRNA and sequencing by DNA method: The procedure that will follow here is essentially that of Tempt et al. mRNA from tracheal culture will be isolated by guanidine isothiocyanate method followed by oligo(dt)-cellulose chromatography. Construction and screening of the DNA library utilizing human antiapomucin will be done as described.

Control in secretion of mucin: The synthesis of mucin in epithelial culture will be followed by 3H glucosamine and 35 SO4 incorporation. The control in synthesis will be studies on transcriptional and translational levels using different inhibitory (acetylcysteine and cyclohexamide) and enhancing (pilocarpine) reagents.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Amendment (Jan 94): Time extended to Oct 94. Additional number of rabbits is required to complete project.

Progress: We have just completed a major study concerning the effects of retinoic acid on mucin gene expression and cellular differentiation in rat and rabbit tracheal expotential cells growing in a serum-tree and hormone-supplemented mechanism. The cells require retinoic acid to differentiate and proliferate normally and is associated with increased mucin gene expression. Without retinoic acid, ten cells did not grow or express mucin gene. When retinoic acid was added back to the medium, the cells grew normally and the mucin gene expression was increased. The increase in retinoic acid-induced mucin gene expression in these cells was inhibited by a mucin antisense oligomer. This study has a potential clinical significance in that combined retinoic acid and antisense oligomer therapy can be developed to treat upper airway respiratory diseases, such as chronic bronchitis, asthma and people exposed to toxic exposures. The estimated completion date has changed from Oct 94 to Sep 95.
Publication:
Manna, B., Ashbaugh, P., Kaufman, B., and Bhattacharyya, S.N. Effect on Retinoic Acid on Mucin Gene Expression in Rat Airways in Vitro. Biochemical Journal (London) 1994, 297:309-313.
Reference:
Bhattacharyya SN, Ashbaugh P, Lund M, Manna B: In vitro effects of drugs on production of mucin in rabbit tracheal epithelial cells expressing mucin gene. Inflammation 16:371-382, 1992.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 90/37A STATUS: Terminated FY94

TITLE: Tracheobronchial Mucins in Health, Disease, and Toxic Exposures

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 90 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): BC Veit

KEY WORDS: Bronchial, Mucin

Study Objective: This proposal has two objectives. One is to prepare a library of mouse monoclonal antibodies against human and rat lung mucin apoprotein to be used as probes for the study of structure and biosynthetic regulation of mucin in tracheal epithelial culture system both at the cellular and DNA level. The other objective is to study the levels and control of transcription and mucin in RNA accumulation in rat tracheal epithelial cells in cultures in response to various noxious agents, like tobacco smoke, ammonia, SO2 and NO2, and different drugs.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: This protocol was written in response to a grant proposal announced by USAMRDC. Since this project was not funded, it has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/08A STATUS: Ongoing

TITLE: Acute Airway Injury and Response: Combined Effect of Smoke and Combustion Products on Mucin Gene Expression and Regulated Mucin Production in the Tracheal-Bronchial Epithelium

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Dec 93 ESTIMATED COMPLETION DATE: Sep 95

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MAJ Nadjem

KEY WORDS: Airway Injury, Smoke

Study Objective: For several years, we at DCI, WBAMC, have studied the characteristics and synthesis of respiratory mucins. One goal, which has now been accomplished, was to study the structure of the protein portion of these macromolecule and raise an antibody against mucin protein core (22). The other goal, now in progress, is to study the regulation of mucin synthesis as well as control of differentiation and proliferation of tracheal epithelial cells in culture (both organ and isolated cell) and ability of different reagents, such as retinoids, different respiratory drugs and mucin antisense oligodeoxynucleotide to intervene effectively with this process and thereby aid patients with chronic as well as acute respiratory problems due to exposure to different noxious substances. To date, we have found that retinoids are required for normal function of tracheal epithelial cells when grown in a serum-free and hormone-supplemented medium. Without retinoic acid, the cells neither expressed mucin message nor maintained normal cytological appearance. When retinoids were added back to the culture medium, the cells grew normally and the mucin message was expressed again (13). Effects of adding pharmacologic agents, such as atropine, histamine, methacholine, phenylephrine, cimetidine, prednisolone and more recently mucin antisense oligodeoxynucleotide to the culture on the growth, differentiation and mucin mRNA level are currently under study -- the most interesting result to date being a marked reduction in mucin mRNA level by prednisolone. In sum, our laboratory, with aid of consultant Dr. Bernard Kaufman of Duke University Medical Center, Durham, North Carolina, is studying the control of production of respiratory mucins on the cellular as well as molecular level and our specific aims of this project are as follows:

1) Study mucin mRNA expression and mucin secretion in rabbit tracheal cultures exposed to smoke (total smoke, filtered smoke and particulate) generated by burning wood and cotton, singly or in combination, in our inhalation chamber in a time and dose dependent manner. Before exposure, the cell culture will be maintained in a serum-free and hormone-supplemented medium with or without retinoids.

2) Examine the extent of injury to the cells by histologic and ultramicroscopic methodology, i.e., whether converted to squamous or more mucus producing cells.

3) Investigate the effect of addition of retinoids to the retinoid-deficient medium on the nature of the cells as well as the mucin message. The reason for studying separately the effect of filtered gases and particulate is to differentiate between two sources so that we can ascertain the extent of injury contributed by each of them and extent of cure process enhanced by retinoids.

4) Study the effect of pharmacologic agents, such as atropine, cromolyn sodium, steroids and mucin antisense oligodeoxynucleotide on the mucin mRNA level as well as on cell differentiation and proliferation of the tracheal culture exposed to smoke as stated above.

5) Study the effect of retinoids and other agents, as described above, on the injury and mucin synthesis and secretion in trachea of whole rabbits exposed to smoke in our nose-only exposure chamber.

6) Produce an immortal mucin-producing cell line by transfecting the primary tracheal epithelial cells with different nonpathogenic viruses.

7) Examine the effect of long-term exposure of smoke on these cells in terms of their differentiation and expression of mucin message and the effect of retinoids and other agents on this process. Primary tracheal epithelial cells in culture stop producing mucins or sometimes do not survive when maintained in culture medium for more than three to four weeks. The immortalized cell lines will provide us with a system to study long-term effect of smoke-related exposure on mucus production and cell injury at the same time.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This project is recently funded by USAMRDC. Work involving smoke exposure has just started. Estimated completion date has been changed from Dec 96 to Sep 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/13A STATUS: Terminated FY94

TITLE: Mucin Type Glycoproteins: Regulated Expression in Normal and Malignant Breast Tissue

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Dec 93 ESTIMATED COMPLETION DATE: Dec 97

PRINCIPAL INVESTIGATOR: Sam Bhattacharyya, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MAJ Nadjem, DA Boman

KEY WORDS: Mucin, Breast Tissue

Study Objective: The long range objective of our study is to define the regulatory processes involved in mucin synthesis and in this proposal, more specifically, MUC 1 expression and the basis for its aberrant expression in mammary malignancies. The specific questions or specific objectives of this study are as follows:

(1) Is the modulation of MUC 1 mRNA due to transcriptional regulators or posttranscriptional stabilization?

Rationale: It appears likely that the site of regulated expression of the polymorphic epithelial mucin (PEM) involved in the aberrant expression of polymorphic epithelial mucin (PEM) in mammary adenocarcinoma (2) is at the mRNA level. The reasons for this explanation are several fold---- first, the primary site of retinoic acid regulation of tracheobronchial mucin production is at the mRNA position as is the pregnancy associated production of casein, PEM and glycan mediated cell adhesion molecule (GlyCAM). The central issue that needs to be addressed is that of whether this regulated MUC 1 mRNA expression is at the level of transcription or at the level of posttranscriptional stabilization of the message. In a number of similar situations, effects on message half life (message stability) have been found to be the primary regulator. The same issue arose in our studies of retinoid regulated tracheal mucin mRNA, and the regulatory process turned out to be considerably more complex than the simple scenario of retinoic acid functioning directly as a ligand mediated transcription factor acting to directly regulate mucin gene expression.

(2) Is the GlyCAM mRNA regulated in the same way as MUC 1?

Rationale: Same as (1).

(3) What is the pattern of MUC 1 mRNA expression during pregnancy, particularly during the involution and subsequent resting phase?

Rationale: There is voluminous literature detailing the development and differentiation of the mammary gland during gestation and the early phase of lactation, which has been driven in large part by its value as a model system to study the hormonal regulation of differentiation. MUCless emphasis has been given to the equally interesting processes that occur during the involution phase following weaning. During the involution phase, there is a dramatic loss of alveolar components, but the epithelium retains a much more elaborate ductal network than that of the virgin.

We only know half of the story of the regulated expression of MUC 1 mRNA. One would expect a decrease in the message levels due to the loss of the alveolar components, but what occurs in the ductal network is uncertain. There could be a marked decrease in expression below the level of the virgin due to the loss of the focal sites of expression (the nests) or the level could be increased due to the more extensive ductal network. It appears unlikely that the expression will return to the same baseline as that of the virgin.

(4) Is MUC1 expression part of the regulatory cascade controlled by retinoids?

Rationale: It is well known that retinoic acid regulates cell proliferation and differentiation in a variety of systems ranging from skin to lung to teratocarcinomas and in many instances the regulatory effects turn out to be complex, with retinoids resulting at the top or near the top of a regulatory cascade. In determining the basis for the aberrant expression of MUC1 mRNA in mammary carcinomas, it would be very important to establish whether retinoid mediated processes are part of the regulatory cascade since the aberrant expression of MUC1 may result from an abnormality in the retinoid regulatory process either at the receptor level or a downstream element.

(5) What are the glycosylation patterns of the carcinoma PEMs in breast malignancies and what is the basis for the malignancy associated unmasking of certain core protein immunodeterminants?

Rationale:

(a) Studies in cell lines and model animal systems are valued experimental approaches to examine the processes involved in MUC1 mRNA expression, because they provide an opportunity to identify and control variables (e.g, control of genetic variables by using "in bred" mice and pulse chase experiments in cell cultures for determining mRNA 1/2 life and message stability). Given the framework of the regulatory processes as determined in these systems, it is then important to return to study of human tumor in a more in vivo situation. While the nude mouse (or scid mouse) in the final analysis is itself a model system, it will provide a way of obtaining the number of malignant samples, grown in an in vivo condition and in the amounts needed to answer our questions concerning the stability of MUC1 mRNA in human mammary tumors.

(b) The observed reactivity with monoclonal antibodies of the SM 3 epitope together with the reactivities of HMFG I and HMFG II epitopes in mammary carcinomas in contrast to reaction only with HMFG I and HMFG II in normal resting and lactating breast has indicated that there is a change in glycosylation pattern in the oncogenic process. Whether the alteration is in the size of the saccharide chains or in the number of substituted thr/ser residues or both is not clear and these are the issues we will address in this study.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This protocol was written in response to a grant proposal announced by USAMRDC. Since this project was not funded, it has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/46 STATUS: Ongoing

TITLE: Use of High Technology to Determine Risk of Drug-Resistant Tuberculosis in the El Paso Region

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 94 ESTIMATED COMPLETION DATE: Oct 95

PRINCIPAL INVESTIGATOR: MAJ William Nauschuetz

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MA Escobedo, L Nickey, VV Tryon, M Lund, GA Handal

KEY WORDS: Drug-Resistant Tuberculosis El Paso, Gene Amplification

Study Objective: Short Range Goals

Mobilize key medical treatment facilities within the El Paso region to recognize the threat of TB and MDRTB: We have already accomplished this goal. The Dept. of Clinical Investigation, WBAMC has agreements with the El Paso City/County Health District and with the El Paso Managed Health Care Consortium (representing four academic institutions and three medical centers) to address the threat of TB and MDRTB in the El Paso region.

Introduce Polymerase Chain Reaction (PCR) technology for the identification of M. tuberculosis and MDRTB: The Dept. of Clinical Investigation, WBAMC is cooperatively working with the El Paso City/County Health District to investigate the sensitivity of PCR compared to routine TB culture and susceptibilities for the detection of M. tuberculosis and MDRTB. We also have an agreement with members of the El Paso Managed Health Care Consortium to share clinical specimens to compare PCR with routine TB culture and susceptibilities.

Intermediate Range Goals

Establish the rate of TB and MDRTB for a stable population in Juarez and for Mexican nationals being treated in El Paso medical centers: Clinical specimens submitted to medical facilities in Juarez for the diagnosis of TB are stained for the presence of acid-fast bacilli. Those specimens that are AFB smear positive are transported to the El Paso City/County Health District for culture confirmation and antimicrobial susceptibilities. However, the sensitivity of AFB smears is about 50%, so many citizens in Juarez are not laboratory-diagnosed properly. By choosing a stable population within Juarez and doing a sweep collection, we can determine the incidence of TB and MDRTB by performing routine culture on all specimens, despite smear results, and by running PCR on each specimen submitted. The PCR should provide a more sensitive method of detecting latent and subclinical TB. We would also use PCR for TB and MDRTB on all Mexican nationals admitted to El Paso medical centers showing respiratory symptoms.

Long Range Goals

The data derived from this study can be used to establish the El Paso region as a high-risk area for TB and MDRTB and as an area that has fulfilled the CDC Task Force Guidelines of implementing high technology for the rapid detection of TB and MDRTB. The data can then be used as a baseline for efficacy studies of newer generation antimycobacterial agents, including those requiring shorter periods of treatment.

Technical Approach: This study is triphasic. In Phase I, primers specific for the amplification of IS6110 will be used for PCR amplification of M. tuberculosis. The primers will be evaluated on ATCC strains of mycobacterial species. If the primers amplify a specific sequence, Phase II will then compare the detection of PCR-amplified M. tuberculosis DNA with standard mycobacteriologic isolation and identification procedures. In Phase III, we will use a primer set that specifically amplifies a 411 base pair sequence from the RNA polymerase gene (rpoB) of M. tuberculosis. Amplification will be done only on pure growth from routin mycobacteriologic media. The 411 base pair fragment that occurs as a result of the amplification will be sent to Dr. Tryon's laboratory at UT-Health Science Center at San Antonio. He will sequence the fragment and determine if mutations indicative of rifampin-resistance are present in the sequence.

Progress: To date, we have identified several problem areas when amplifying M. tuberculosis form clinical specimens:

- specimen prep, including cell lysis, can be difficult
- different primer sets greatly alter results

We have decided to amplify using primers specific for IS6110 and for mpt 40. We have made these primers labelled with biotin and TBR, which allows us to assay test results on our QPCR 5000, rather than having to rely on agarose gels.

We are evaluating two simple, clinically applicable methods for release of amplifiable nucleic acid. These methods are (a)boiling and (b) Gene ReleaserTM.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 88/04 STATUS: Completed FY94

TITLE: Activation of T-Cell Subsets in Bermuda Grass Allergy Patients

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 87 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: Bruce C. Veit, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Smiley, S McIntyre

KEY WORDS: Allergy, T-cells subsets, Immunoregulation

Study Objective: To determine whether there are detectable changes in numbers and functions of manifestations of Bermuda grass allergy. Since T4+ cells are associated with helper/inducer functions and T8+ cells are associated with cytotoxic/suppressor functions, alterations in the numbers of T4+ or T8+ activated T cells may correlate with changes in the immunoregulatory processes involved in controlling the allergic state. Peripheral blood samples will be obtained from patients during active allergy, immunotherapy, and disease quiescence. Samples will be analyzed by 2-color flow cytometry and by immunohistochemical staining for the distribution of T4+ and T8+ cells and the percentage of activation antigen-positive cells within each of these subsets. T cell subsets will also be analyzed for their ability to increase or suppress the synthesis and/or secretion of IgE. Serum samples from these patients will be analyzed for the presence of soluble IL-2R (circulating IL-2 receptor). These studies should improve our understanding of the immunoregulatory processes involved in the control of IgE-mediated allergic responses.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: This protocol has been completed.

Abstract: In order to determine whether immunotherapy of Bermuda grass allergy patients results in the development of suppressor cells, lymphoproliferative responses were measured in peripheral blood lymphoctyes from Bermuda grass allergy patients and in short-term (<2yrs) and long term (>2yrs) immunotherapy patients. Peripheral blood lymphocytes were co-cultured in the presence or absence of the putative suppressor cells which were obtained by incubation of autologous peripheral blood lymphocytes for 2 days with Bermuda allergen followed by mitomycin C-treatment. Suppressor cell activity to Bermuda allergen was not detectable in any of the patient groups tested. However, parallel studies of response to ragweed allergen in the same patient groups revealed significant suppressor cell activity in the ragweed allergen-short term immunotherapy group. Comparative studies of the components of the suppressor cell assay revealed that, at optimal mitogenic concentrations, Bermuda allergen had a much greater stimulation index than did ragweed allergen. Reducing Bermuda allergen concentration 5-fold below that required for optimal stimulation resulted in the detection of suppressor cell activity in Bermuda grass allergy-short term immunotherapy patients. Flow cytometric analysis of Bermuda grass allergy-suppressor cell populations (at optimal mitogenic concentration of Bermuda allergen) revealed an increased percentage of CD4+/IL-2R+T cells and decreased percentages of suppressor-inducer cells and CD8+T cells (presumably suppressor T cells). The proliferative response of autologous responders cells in the presence of suppressor cells exhibited statistically significant correlation with duration of immunotherapy: low response in normals and long term immunotherapy patients and high response in allergy patients and short term immunotherapy patients. Plasma allergen-specific IgE levels and CD4+/IL-2R+ T cell levels correlated well with immunotherapy course: the levels of each decreased as length of immunotherapy increased. These results suggest that Bermuda grass allergy-specific IgE synthesis may be down-regulated by a suppressor cell mechanism.

However, proliferative responsiveness of suppressor cells rather than suppressive activity, appears to correlate more closely with immunotherapy outcome.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/04 STATUS: Ongoing

TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: Bruce Veit, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Breast Cancer

Study Objective: The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanism(s) of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer.

Technical Approach: The proposed research program consists of three approaches:

(1) Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemotherapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; and (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations.

(2)Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc); use of flow cytometry on single-cell suspensions and immuno-histochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3)Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; and (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemo-cytotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility during cell cycle.

Progress: To date, we have analyzed nine primary human breast carcinoma biopsies (one of which also had an accompanying lymph node), eight normal breast tissue samples and one tumor which was grown in immunodeficient (nude) mice. Analyses of primary breast biopsies by flow cytometry and digital image analysis are being utilized to study cell cycling and ploidy in these samples. In addition, progesterone, estrogen, and epidermal growth factor receptor, HER-2/neu, Ki-67, PCNA, transforming growth factor, and insulin-like growth factor expression are also being measured in these tissue biopsies. Parallel studies are also being carried out in established human breast carcinoma cell lines as well.

Studies of apoptosis are also ongoing. These studies utilize three human breast carcinoma cell lines, DU4475, BT-474, and SK-BR-3, which are maintained in continuous in vitro culture by serial passage. One of these cell lines, BT-474, requires insulin for optimal growth. It was predicted that removal of this growth factor would result in the initiation of apoptosis (or at least necrosis). However, results of controlled growth studies of insulin-deficient BT-474 cell cultures indicated that either insulin is not an essential growth factor requirement for these cells or that there may be autocrine synthesis of insulin by these cells. We are utilizing an in situ labelling technique to detect DNA fragmentation as a function of apoptosis. This method involves the terminal attachment of digoxyenin-dUTP to 3'-OH ends of nucleosome-sized DNA fragments followed by an antidigoxygenin antibody conjugated to a reported enzyme (for immunohistochemical studies) or to fluorescein (for flow cytometric studies). Parallel studies are also being carried out with capillary electrophoretic analyses to quantitate numbers and sizes of DNA fragments. Micromolar or nanomolar concentrations of 5-azacytidine, dexamethasone, staurosporine, camptothecin, and amsacrine present in cell cultures for 4 to 6 hours induce significant levels of detectable apoptosis. Additional studies of other drugs, i.e., 5-fluorouracil, cyclophosphamide, and doxorubicin will also be undertaken to determine their ability to initiate apoptosis and to interfere with growth factor-induced cell cycling.

We have obtained several other human breast carcinoma cell lines from American Type Culture Collection and will continue our search for a cell line that has an essential requirement for exogenously provided growth factor (paracrine) to be used as a model for studying the induction of apoptosis resulting from growth factor deprivation.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/05A STATUS: Ongoing

TITLE: Growth Dynamics of Breast Cancer Cells: A Study of Growth Regulatory Factors using the Murine Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: Bruce Veit, PhD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K Nauschuetz

KEY WORDS: Breast Cancer

Study Objective: The aim of this project is to study the biological properties of breast cancer cells as they relate to intra- and extra-cellular growth factor signaling, cell cycle progression, and mutational changes which occur during tumor cell growth as the result of growth factor and chemotherapeutic influence. Information gained from this study should provide a better understanding of the mechanisms of breast tumor cell resistance and a rationale for applying appropriate therapeutic methods to the treatment of breast cancer. Our studies will attempt to answer the following questions: (1) What are the phenotypic and biological characteristics of variant sublines within breast cancers? (2) Do human breast tumors that grow in thymic nude (nu/nu) mice retain their histological grade and variant subline profiles? (3) What are the selective pressures which create heterogeneity in breast cancers? (4) Do breast cancer relapses occur because of physiological (non-genetic) or mutational (genetic) alterations in growth factor signaling pathways? (5) Do normal stromal cells exert growth regulatory influences on tumor cells via growth factor secretion and/or cytokine production? (6) Does growth factor deprivation of growth factor-dependent tumor cells result in the initiation of apoptosis?

Technical Approach: The proposed research program consists of three approaches:

(1)Study of in vitro cultured breast cancer cell lines which express a variety of growth factor receptors, tumor-associated antigens and tumor suppressor genes or proto-oncogenes for (a) outgrowth of mutant clones as a function of selective pressure by chemo-therapeutic agents, growth factors and cytokines; (b) responsiveness to a variety of growth factors and mitogens; (c) altered expression of cell-surface antigens; (d) changes in ploidy, S-phase fraction, nuclear antigen expression, and cell cycle variations.

(2)Study of primary isolates of breast tumors (benign and malignant) from patients upon initial diagnosis and at relapse for (a) cellular content of tumor cells, stromal cells, and infiltrating cells (i.e., lymphocytes, monocytes, etc.); use of flow cytometry on single-cell suspensions and immunohistochemical/immunofluorescence image analysis on tissue sections and (b) tumor cell heterogeneity with respect to tumor-associated antigens, growth factor receptors, DNA content (ploidy, S-phase fraction) and cell-cycle variations.

(3)Study primary isolates of malignant breast tumors (at initial diagnosis and at relapse) in vivo in nu/nu mouse xenografts for (a) growth response and selective pressure of chemotherapeutic agents, growth factors and cytokines; (b) alterations in cellular content of tumor cells, stromal cells and infiltrating cells during growth progression and modification through the use of growth factors, chemotherapeutic agents and cytokines; (c) emergence of chemotherapeutically resistant tumor cells and their characterization with respect to growth factor responsiveness; (d) mechanisms of tumor cell death: use of agents (growth factors or inhibitors) which induce cells to enter cycle or inhibit them from entering cycle in combination with chemo-cytotoxic agents to determine whether cell death occurs via apoptosis or as the result of increased susceptibility during cell cycle.

Progress: We have attempted to implant into immunodeficient (nude) mice and obtain growth of 1mm pieces of primary human breast carcinoma biopsies from four patients. In all cases, we were unsuccessful in obtaining in vivo growth of these xenografted tumors. We have also attempted to obtain growth of several human breast carcinoma cell lines in these immunodeficient mice. Of five cell lines tested, we were able to obtain growth of two (DU4475 and BT-474) in these mice. Whereas 1 x 105, 5 x 105, and 1 x 106 cells injected subcutaneously did not result in tumor growth, it was determined that 1 x 107 cells were required in order to obtain progressive growth. We will continue to explore the ability of other human breast cancer cell lines obtained from American Type Culture Collection to produce progressive tumor growth in the immunodeficient mouse model. Once established, this model will then be used to study growth factor and chemotherapeutic drug influences on the in vivo growth and evolution of breast cancer cells. Our mouse studies will most likely be impeded by purchase and maintenance of the immunodeficient mice. During this period October 1, 1992 through September 30, 1994, this project was externally funded and the purchase and maintenance costs for these mice were covered by those funds. Although the period for reporting on this project has been extended to December 1995 by MRDC, a request for a no-cost extension on spending the funds was not approved. Therefore, payment of these costs must come from other sources. The estimated completion date has changed from October 1995 to December 1995.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 83/37 STATUS: Ongoing

TITLE: Cardiopulmonary Effects of Stressful Exercise at 4,000 Feet on SCT Individuals

MONITOR (applicable for projects reviewed semi-annually): MAJ Lynn Keenan

START DATE: Jul 84 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Sickle Cell Trait, Stress, Hypoxia, Exercise

Study Objective: To establish baseline pulmonary function data (spirometry, helium dilution lung volumes, maximum voluntary ventilation L/min (MVV), arterial blood gas analyses (ABG), single breath diffusing capacity DLCOSB (ml/min/mmHg) and steady state

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Addendum (Mar 85): Added testing at 7,500 ft

Progress: Semi-Annual Review (Apr 94):120 subjects were tested. Data collected at simulated 4,000 m (Phase III) is being evaluated.

Annual Review: No progress was reported by principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 88/38 STATUS: Ongoing

TITLE: Comparison of Physiologic Responses to Prolonged Exercise Simulating Army Field Training in Sickle Cell Trait and Controls (Phase IVa)

MONITOR (applicable for projects reviewed semi-annually): MAJ Lynn Keenan

START DATE: Jul 89 ESTIMATED COMPLETION DATE: 1995

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos, J Little, TW Martin

KEY WORDS: Sickle cell trait, Endurance exercise

Study Objective:

1. To determine if submaximal (50-70% VO2 max) prolonged treadmill exercise (1 hour 30 minutes) with a final maximum exercise (5 minutes), similar to Army field training conditions, would elicit differences in exercise performance between Sickle Cell Trait (SCT) and control volunteers.
2. To evaluate changes in Percent Sickling (%S) and blood viscosity with prolonged exercise in SCT volunteers and to analyze their relationship to venous oxygen saturation, hydration status and temperature.
3. To assess biochemical and enzymatic changes in blood and urine that would suggest muscle damage (rhabdomyolysis) during prolonged exercise.
4. To compare the effect of prolonged exercise on renal function in SCT and controls.
5. To determine whether subtle pulmonary microcirculatory abnormalities not present at rest would be detected during exercise in SCT compared to controls.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): A total of 16 patients have been enrolled. No new patients were enrolled during this review period.
Annual Review: Three abstracts have come from this work that have been submitted previously. The final manuscript, however, will be written this year.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/68 STATUS: Completed FY94

TITLE: In Vivo Sickling in Sickle Cell Trait (HbAs): Effect of Hypoxia, Exercise and Red Cell Sampling/Fixation Time

MONITOR (applicable for projects reviewed semi-annually): LTC James Wallingford

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Feb 94

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

KEY WORDS: Sickle Cell Trait, Sickling Kinetics, Sickling and Exercise, Sickling and Hypoxia, Sickling Methodolgoic.

Study Objective: Recent discoveries in Hemoglobin S (HbS) polymerization kinetics make it imperative to re-examine the sickling phenomenon in vivo in order:

1. To corroborate, by using a new, specially designed blood drawing technique, that in vivo sickling is present in the blood of individuals with Sickle Cell Trait.
2. To determine the effect of hypoxia on the magnitude of sickling.
3. To compare the combined effect of hypoxia and exercise on sickling measured in effluent blood from an exercising limb and in arterial blood that has recirculated through the lungs during leg exercise.
4. To determine the effect of red cell sampling/fixation time on the measurement of percent sickling.

Technical Approach: The study will be carried out in the Human Performance/SCT Laboratory at William Beaumont Army Medical Center in El Paso, Texas at an altitude of 1270m and mean barometric pressure of 656mm Hg.

Ten individuals with SCT will be used for this study. All will be between 18 and 28 years of age and will be non-smokers. Volunteers will be obtained from the basic training reception station at Logan Heights, Ft Bliss, Texas similar to previous studies (WBAMC 83/37, WBAMC 88/38). All incoming recruits are screened for SCT with a Sickledex test; positive results will be confirmed by cellulose acetate (pH=8.4) hemoglobin electrophoresis with % HbS determined by quantitative scanning densitometry. Individuals identified as possessing SCT (HbAS) will be asked to participate in the study after an explanation of the protocol, including its purpose, risks and benefits by one of the researchers. Based on past experience, between 30-50% of basic trainees with SCT will volunteer to participate. In addition, SCT counseling will be provided by COL Weisman. This remains important because >70-80% of basic trainees with SCT do not know that they have HbAS or what it means to be positive for HbAS. If the individual with SCT agrees to volunteer in the study, he or (they) will be transported to the SCT lab. Upon arrival, the subjects will read the volunteer agreement and ask any remaining questions. We will explain that they may withdraw from the study at anytime without penalty. If the volunteer withdraws, he will be transported back to his original unit. The NCO will not be informed of the circumstances surrounding the trainee's return. Usually within hours, the former volunteer and the rest of his unit is transferred to a training battalion and a new NCO.

After obtaining informed consent, documented in writing, a physical examination will be performed on each volunteer, and a medical history will be obtained. Baseline EKG, CBC, Urinalysis and SMA-20 will be obtained/checked. If the subject has no contraindication to exercise, he will be accepted into the study. Controls are not necessary for this study.

A 20 gauge venous catheter (3.2 cm length, Quick Cath, Travenol Labs) will be inserted into one of the median antecubital veins of the exercising arm of each volunteer. If an Allen's test reveals a palmar blush within five seconds, a second 20 gauge catheter (Becton, Dickinson) will be placed in the radial artery of the non-exercising arm. Using this technique in over 150 arterial catheter insertions, we have had no ischemic

complications; all volunteers have successfully completed basic training. Approximately 30-40% of subjects have experienced minor wrist discomfort which typically resolved within 24 hours without sequelae. No other complications have occurred. Previously approved WBAMC Protocol 88/38 fully discusses the risks of catheterization. The patency of the catheters will be maintained using a heparin flush solution (10 USP unit/ml) intermittently. Blood samples will be drawn anaerobically for blood gas analysis and percent sickling measurements at rest and during exercise.

This is a simplified version of previously approved WBAMC protocols 83/37 ("Cardiopulmonary Effects of Stressful Exercise at Altitude (4000ft) of Individuals with Sickle Cell Trait (SCT) with modification to include altitudes of 2300m and 4000m") and WBAMC 87/25 ("Axillary Venosis Sickling in Individuals with Sickle Cell Trait During Upper Extremity Exercise in a Hypoxic Environment").

The subjects will be studied at rest breathing room air FIO2=21%, PI02=127mmHg) and then breathing a hypoxic gas mixture (FI02=14%, PI02= 85mmHg) equivalent to 4000m for 15 minutes at rest (before the exercise) and during the exercise tests. The hypoxic gas will be administered via a respiratory gas mask during rest and hand grip exercise and a mouth piece during leg exercise. The inspiratory port of both devices will be connected to a 120L reservoir bag continuously fed from the gas cylinder with the hypoxic gas.

Two types of exercise formats will be used:

a) Hand Grip Exercise: After 15 minutes of breathing the hypoxic gas mixture, the subjects will first perform a maximum rhythmic hand grip exercise at a rate of 60 grips per minute, pulling a weight of 16 pounds from an apparatus, consisting of a hand grip cable, pulley and adjustable weights. The exercise will be performed only with the arm in which the venous catheter has been placed. The duration will be approximately 3 minutes.

b) Leg Exercise: After 15 minutes of breathing the hypoxic gas mixture at rest, the subjects will be exercised on an electronically braked cycle ergometer. The exercise test will consist of two stages of steady state exercise consisting of 5 minute duration each. The first stage will be at 50%, and the second at 75% of the maximum power predicted for each individual. During the cycle exercise test, minute ventilation (VE), oxygen uptake (V02), carbon dioxide production (VC02), and respiratory exchange ratio (R) will be measured in a breath-by-breath fashion using a computerized system (Medical Graphics Corporation) that integrates flow (pneumotachometer) with the respiratory gases measured continuously in the mouthpiece with a mass spectrometer (Perkin-Elmer). Heart rate (HR) and electrocardiographic changes will be monitored continuously during the exercise tests with an Electrocardiographic System. The arterial blood gas results will be entered in the computer and the physiologic dead space-tidal volume ratio (VD/VT) and the alveolar-arterial oxygen pressure difference [P(A-a)02] will be calculated.

A short IV extension tube attached to a drawing apparatus will be connected to either the venous or the arterial catheter. The apparatus consists of the following elements: (a) a 3-way stopcock connected in series with (b) a one-way back pressure valve placed between the venous catheter and the port where (c) the syringe with the 1% glutaraldehyde phosphate buffer solution will be connected (a 6cc plastic syringe will hold the glutaraldehyde solution). A (d) plastic safety sleeve will be placed around the plunger and then marked with (e) a red ring. The 1% glutaraldehyde solution is a biological fixative used for fixing blood cells. If this solution is injected into the subject, it could induce serious medical complications. To our knowledge, there is no literature available about the effect of accidental injection of glutaraldehyde into a human being.

The drawing apparatus has been tested for safety by the Clinical Pharmacist of the Hematology/Oncology Service, WBAMC (see attached report). It would appear that this apparatus/technique approaches almost complete freedom from the possibility of accidental injection of the fixative into the subject; This possibility is even less likely if used by a researcher who is familiar with the system. Another important safety feature is that during the blood sampling, all the maneuvers that are required will be that of pulling the plunger, and never that of pushing or injecting.

Arterial and venous blood samples will be taken at rest breathing room air, at rest breathing the hypoxic gas mixture (14% FIO2), and at the end of the hand grip and leg exercises, while breathing the hypoxic gas mixture. The blood samples will be drawn and then fixed immediately in the fixative solution (<2sec); immediately thereafter, another blood sample will be collected into a heparinized syringe. This syringe will then be removed from the drawing apparatus, and the blood fixed in glutaraldehyde solution at 30, 60, 180, and 300 second intervals, while being maintained in an anaerobic environment at 37oC. At the end of the Exercise test, the catheters will be removed.

Blood gas analysis will be performed on all samples collected including those used for the measurement of Percent sickling. Oxygen tension, carbon dioxide tension and pH will be measured in an automated blood gas analyzer (IL) and oxygen saturation in a spectrophotometric oximeter (IL CO-Oximeter).

After fixation of the blood samples, slides will be prepared from one to two drops of the glutaraldehyde-red cell suspension and examined under a phase contrast microscope. A thousand cells from random areas of the preparation will be photographed for determination of percent sickling (number of sickled cells per 100 counted). Sickling will be determined independently and in a blind fashion by two observers. A cell will be considered sickled if it is elongated with at least one or two projections or if it is irregularly shaped with an angle and one or more points (21). Ovalocytes, tear drops, echinocytes, and other poikilocytes will be excluded. These criteria for sickling morphology have been adopted and vigorously applied in our lab (22).

An ACLS-qualified physician will monitor the patient's clinical status during the test. Testing will be interrupted if the patient experiences significant discomfort (abdominal pain, muscle cramps) or if a dysrhythmia is noted. A crash cart, supplemental oxygen and defibrillator will be available at all times. In over 150 prior cycle exercise tests with hypoxia we have had no significant complications. We anticipate the catheters will be in place for no longer than two or three hours. After the tests are completed, the catheters will be removed immediately and direct pressure will be applied to the site. A stat vascular surgery consult will be obtained in the unlikely event that a subject develops signs of ischemia.

Progress: Semi-Annual Review (Apr 94): No new patients were enrolled during this review period.
Annual Review: Protocol has been completed. There have been fourteen subjects entered in this study wih no noted adverse reactions. Three abstracts have come from this work that have been submitted previously. The final manuscript, however, will be written this year.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/34 STATUS: Ongoing

TITLE: Comparison of Anaerobic Power Between Female and Male Soldiers

MONITOR (applicable for projects reviewed semi-annually): LTC Larry Tremper

START DATE: Jun 93 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

KEY WORDS: Anaerobic Exercise, AIT Anaerobic

Study Objective:

(1)To measure the anaerobic power for lower and upper body exercise in male and female soldiers, and develop a data base that may be used as a reference to gauge performance levels of anaerobic power.

(2)To determine the impact of intense anaerobic work on cardiopulmonary functions.

Specific Objectives:

° To determine if the U.S. soldier is more fit to perform anaerobic exercise using upper or lower body exercise.

° To compare the level of anaerobic power of female with male soldiers.

° To study the changes in cardiopulmonary physiology during and after intense, all-out anaerobic work.

° To apply these results to different military operational field tasks so that specific training standards can be appropriately modified if necessary.

Technical Approach: Prospective study. The same volunteers will be used as their own control. All subjects will undergo the same treatment (AIT) and testing protocols.

Progress: Semi-Annual Review (Apr 94): Amendment submitted to delete Ariel Linden and Dr. Roger Belbel as associate investigators, to include females, and to change certain aspects of exercise tests.
Annual Review: The estimated completion date has changed from Dec 94 to Jun 95. Four subjects were entered in the study with no noted adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/44 STATUS: Terminated FY94

TITLE: Early Cardiopulmonary Exercise Abnormalities in Asymptomatic Smokers

MONITOR (applicable for projects reviewed semi-annually): LTC Larry Tremper

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Jan 96

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

KEY WORDS: Exercise Abnormalities Asymptomatic

Study Objective:

1. To recruit a group of asymptomatic smokers with at least a 15 pack years smoking history and normal spirometry and carefully match them by age, race, and activity level to a comparable group of non-smokers. Both groups will be well characterized based on extensive health questionnaire responses, complete baseline PFTs (spirometry, lung volumes, diffusing capacity of carbon monoxide [DLCO], selected "small airway" tests), bronchial hyperactivity testing and coronary risk stratification analysis. The results of previous studies (Cooper et al 1968, Daniels et al 1984, Sue et al 1985) that have attempted to evaluate cardiopulmonary differences between smokers and non-smokers were clouded by poor characterization of the populations studied with respect to: level of physical activity, carboxyhemoglobin (COHb) level, concurrent conditions, abnormalities of resting PFTs, and description of symptoms, etc.

2. To determine whether maximal exercise testing is an effective diagnostic tool for the early detection of cardiopulmonary abnormalities in asymptomatic smokers.

a. To determine if exercise capacity as determined by a VO2 max and by 2 mile run time is different between asymptomatic smokers and non-smokers (Daniels et al 1986, Bahrke et al 1986) when physical activity level and COHb are controlled.

b. To determine whether other more subtle differences in the cardiopulmonary response to exercise can be detected between asymptomatic smokers and non-smokers. These may include pulmonary gas exchange abnormalities (Frans et al 1975) and abnormal tidal flow-volume loop differences as indicators of early expiratory flow limitation which in asymptomatic smokers may only be seen at maximal exercise. Both of these types of abnormalities would possibly be reflective of "peripheral airways" dysfunction. Also, subtle cardiovascular patterns suggestive of occult heart disease may also be discerned.

3. To relate the cardiopulmonary abnormalities observed in asymptomatic smokers to various components of the health questionnaire including smoking history, activity level, coronary risk analysis, etc. and to resting PFTs and results of a bronchial hyperactivity testing.

4. To generate a data base of asymptomatic smokers with and without abnormal cardiopulmonary response to exercise.

Technical Approach: Prospective controlled study.

Progress: Semi-Annual Review (Apr 94): No new patients were enrolled during this review period.
Annual Review: Protocol was terminated because it was not funded.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/57 STATUS: Ongoing

TITLE: Effect of ATROVENT® in Exercise Performance in Patients with Chronic Pulmonary Disease

MONITOR (applicable for projects reviewed semi-annually): LTC Larry Tremper

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Dec 94

PRINCIPAL INVESTIGATOR: COL Idelle M. Weisman

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RJ Zeballos

KEY WORDS: Chronic Pulmonary Disease (CPD), ATROVENT®

Study Objective: Ipratropium bromide (ATROVENT®) is an anticholinergic agent with well established bronchodilative properties in patients with chronic obstructive pulmonary disease (COPD) (NEJM 1993;328:1017-22). Ipratropium treatment also reduces the volume of sputum without altering its viscosity (Chest 1991;86:871-6). Recent in vitro evidence also suggests that ipratropium may have anti-inflammatory effect (Rennard, Personal Communication).

Improved airway patency observed after inhalation of ipratropium may also lead to a decrease in static lung volumes, in particular, trapped air volume (TAV) (Brit Med J 1988;297:1506-09). This, in turn, may lead to decrease in work of breathing and a decrease in dyspnea, including exertional dyspnea.

Thus, chronic administration of ipratropium, in patients with COPD may lead to the increase in alveolar ventilation and consequent improvement in oxygen saturation and possible attenuation of the inflammatory process, well documented in lungs of patients with COPD. These physiological improvements may be particularly important during exercise. However, the effect of chronic dosing with ipratropium on exercise tolerance was only rarely studied (Am Rev Respir Dis 1992;145:A758).

Thus, in this study we will examine effect of chronic treatment with ipratropium MDI on exercise tolerance in COPD patients.

Technical Approach: A double-blind, randomized, placebo-controlled, two-arm parallel multi-center study.

Progress: Semi-Annual Review (Apr 94): Seven patients were enrolled. There were no adverse events to report. Annual Review: Eleven subjects were successfully entered into this protocol with no noted adverse reactions. Data analysis will be performed in CT. This study is part of a multi-center (at least 10 centers) study. Randomization has not yet been broken. Estimated completion date has changed from Apr 94 to Dec 94.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/48 STATUS: Terminated FY94

TITLE: Practical Value of Hyper-Reactive Airway Testing in the Assessment of Asthma in Army Recruits

MONITOR (applicable for projects reviewed semi-annually): LTC James Wallingford

START DATE: Aug 89 ESTIMATED COMPLETION DATE: Jul 95

PRINCIPAL INVESTIGATOR: R. Jorge Zeballos MD

DEPARTMENT: DCI FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): IM Weisman

KEY WORDS: Asthma, Ait, Army Recruits, Reactive Airway Disease, Brochial Challenges

Study Objective: 1. To determine whether a screening test for hyperactive airways "asthma" should be established for individuals who, although having met entry requirements as specified in AR 40-501-2-24d have allergic histories and/or a history of asthma in childhood (HAC), which would appear to increase their likelihood of exercise induced asthma and other asthma related problems during basic training.

2. To determine which of the currently available methodologies, for the diagnostic evaluation of hyperactive airways, would be most accurate (high sensitivity, high specificity), practical, and cost effective for the screening of potential Army recruits.

3. To modify standard methods for the diagnosis of airway hyperresponsiveness so as to make them more suitable to the Military Entrance Processing Service (MEPS).

4. To propose modification for AR40-501-2-24d based on the results of this study and thereby reduce the number of Existing Prior to Service (EPTS) discharges secondary to asthma.

Technical Approach: All incoming basic trainees at Ft. Bliss will be asked to respond to a questionnaire which will identify the inclusion criteria: (1) history of allergic rhinitis (hay fever), and/or (2) history of allergic dermatologic disorder (i.e., eczema), and/or (3) history of asthma in childhood and (4) normal or border line pulmonary function tests. Service members responding affirmatively to any of the inclusion criteria will be asked to participate in the study.

A physical examination will be performed on each volunteer, and a medical history will be obtained. Baseline EKG, CBC, Total Eosinophil count, and SMA-20 will be obtained/checked.

The study will be conducted on 2 consecutive days in the Human Performance/ Pulmonary Function Labs at WBAMC. On the first day, the exercise induced broncho- constriction test will be performed in the morning, followed by the nebulized distilled water test in the afternoon. On the second day, the hyperventilation with cold air test will be performed in the morning, followed by the nebulized methacholine test in the afternoon. The pulmonary functions at baseline for each test should not differ by more than 5%. The volunteers will be followed during their stay at Ft. Bliss (at least 7-8 weeks) and even longer for those SM's assigned here for AIT. All admissions to a hospital for 48 hours or more, failures to pass the Army Physical Fitness Test, or discharge from the service (especially with a principal diagnosis of asthma) will be carefully documented. A relationship between positivity to hyperactive airway tests and medical problems related to asthma will be analyzed.

An ACLS-qualified physician will monitor the patient's clinical status during all the testing. Testing will be interrupted if the patient experiences significant chest tightness, wheezing, shortness of breath, chest pain, or if a dysrhythmia is noted. A crash cart, supplemental oxygen and defibrillator will be available at all times.

Progress: Semi-Annual Review (Apr 94): No new enrollments. Investigators are working on methodology and have conducted pilot studies thus far.
Annual Review: Protocol was terminated because it was not funded.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/20A STATUS: Ongoing

TITLE: Comparison of Osseointegration of Titanium Implants in Cranial and Iliac Autologous Bone Grafts Stabilized with Immediate Titanium Implant Fixtures in Miniature Swine

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 91 ESTIMATED COMPLETION DATE: Dec 94

PRINCIPAL INVESTIGATOR: LTC Nathan C. Dickerson

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MG Donovan

KEY WORDS: Titanium Implants, Canial Bone Grafts, Iliac Bone Grafts, Onlay Bone Grafts

Study Objectives:

1. Examine time interval of osseointegration of titanium implants when placed in immediate bone grafts.
2. Compare the rate of osseointegration, i.e., success rate, of titanium implants in immediate autologous calvarial and iliac bone grafts.
3. Compare the rate of osseointegration, i.e., success rate, between immediate placement of titanium implants in grafted bone to titanium implants in mature bone grafts.
4. Determine the recommended time interval of osseointegration required prior to placement of functional load on implants.

Technical Approach: Six miniature swine will be used for this study. Each animal will serve as its own control by having an implant placed in a non-grafted facial bone site.

Under general anesthesia, each swine will have autologous bone from the outer table of the frontal and parietal bones harvested and a corticancellous bone graft from the iliac crest harvested. Placement of the bone grafts will be to the nasal bones of the swine. The bone grafts will be rigidly fixed utilizing one or more Branemark titanium implant fixtures of 7mm or 10mm lengths.

Four calvarial bone grafts and four iliac bone grafts will be utilized on each animal. The calvarial bone grafts will be on the right side and the iliac bone grafts will be on the left side of the nasal bones.

One swine will be euthanatized at one month, two months, four months, six months, eight months, and twelve months to obtain specimens for histological studies. Twenty-one days prior to scheduled euthanation and biopsy, the animals will be marked with an I.M. injection of a tetracycline derivative to assess new bone growth in the bone grafts adjacent to the implant fixtures. Barium sulfate mixed with heparinized formalin will be infused after euthanasia to mark neovascularization in the bone grafts.

Each bone graft site will be physically measured for evidence of bone resorption or growth, and these measurements will be compared with the dimensions of the bone grafts measured at time of initial placement. The titanium implants are of fixed length and will serve as markers for loss or maintenance of the bone graft heights along with the above physical measurements.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: There has been 10 subjects entered in this study with no noted adverse reaction. Necropsies have been completed and histological specimens are processed. Extensive efforts are being done to obtain data for statistical analysis. It is expected that data collection is to be completed by 1 Oct 94 and an abstract ready for publication by the end of 1994. The estimated completion date has changed from Jan 94 to Dec 94.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/37 STATUS: Ongoing

TITLE: Bone-Anchored Craniofacial Prostheses Investigation

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: COL Michael G. Donovan

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Gary, N Dickerson

KEY WORDS: Implants, Bone-anchored Prostheses

Study Objective:

1. To evaluate the long term retention success rate for titanium implants anchoring craniofacial prostheses.
2. To evaluate the long term stability of the prostheses.

Technical Approach: Patients will be admitted to Ward 6W, and have the routine pre-surgery laboratory studies, to include blood work, x-rays and urinalysis, and any further tests required that would be dictated by their medical history. Appropriate referrals will be given to various medical specialties if indicated. The surgery to implant the prosthesis will be conducted in the operating room. Anesthetic will be given to minimize the pain that is associated with any surgical procedure. The doctor will cut the skin covering the area to be treated and then drill holes in the bones of the face, head, or both. Next, tiny titanium fixtures will be inserted into the holes, the skin will be replaced so that it covers the fixtures, and the skin stitched. The titanium fixtures will be left in place for 3-4 months to allow them to become integrated with the bone. During this time the patient will visit the doctor 2-3 more times so their condition can be monitored.

After 3-4 months, the patient will once again be admitted to the hospital, where they will undergo additional surgery. After the anesthetic is administered, the doctor will again cut the skin covering the area being treated. Some of the tissue under the skin will be removed and the skin will be stitched back together. The doctor will then puncture the skin directly over each implanted titanium fixture and will attach a small skin-penetrating abutment to each fixture. For 3-4 weeks, the treated area will be allowed to heal. During that time the patient will visit their physician 1-3 times so that their condition can be monitored.

After 3-4 weeks, a prosthesis will be made and will be attached to the anchors. After the prosthesis is in place, the patient will continue to visit their physician 3 times during the first year, then twice a year, so that their condition can be monitored, as well as their level of satisfaction.

Progress: The FDA along with Nobelpharma have not closed this study as data is presently being obtained for this multi centered study. Another subject was added retroactively to this study as per Nobelpharma's request to the FDA, and data is being collected for this patient. This institution's clinical investigation service has the correspondence for this action. There have been 5 subjects entered in this study with no noted adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/38A STATUS: Ongoing

TITLE: Evaluation of Osseointegration of Immediately Placed Titanium Implant Fixtures in Allogeneic Onlay Bone Graft in Miniature Swine

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Jul 96

PRINCIPAL INVESTIGATOR: MAJ Trent C. Filler

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Donovan, N Dickerson

KEY WORDS: Titanium Implants

Study Objective: To examine if osseointegration of titanium implants occurs in allogeneic onlay bone graft when placed immediately using the concepts of tissue guided regeneration; to examine time interval of osseointegration of titanium implants when placed immediately into allogeneic onlay bone graft using the concepts of tissue guided regeneration; to compare rate of osseointegration, i.e., success rate between placement of titanium implants in allogeneic grafted bone to titanium implants placed in autogenous bone grafts (study #92/20, Comparison of Osseointegration of Titanium Implants in Cranial and Iliac Autologous Bone Grafts Stabilized with Immediate Titanium Implant Fixtures in Miniature Swine); and to determine the recommended time interval of osseointegration required prior to placement of functional load in implants placed in grafted allogeneic bone.

Technical Approach: Fifteen miniature swine will be used for this study. Up to three animals will serve as a source for the allogeneic calvarial and iliac bone grafts to be grafted to the other twelve animals. The long bones from these three animals will serve as a source for Demineralized Bone Powder. The bone will be harvested and then processed by the Department of Anatomy, Medical College of Georgia and the protocol on Appendix A.
Under general anesthesia each of the twelve swine will have allogeneic bone from the frontal and parietal region and allogeneic bone from the iliac crest grafted to the nasal bones, maxilla and mandibular. The allogeneic bone grafts will be augmented with bone morphogenic protein. The bone grafts will be rigidly fixed utilizing one or more Branemark titanium implant fixtures of 10 mm length and Luhr rigid fixation screws.

Five calvarial bone grafts and five iliac bone grafts will be utilized on each animal. The calvarial bone grafts will be on the right side, and the iliac bone grafts will be on the left side of the nasal bones, lateral maxilla, and mandibular ramus.

Two of the calvarial bone grafts and two of the iliac bone grafts will be covered with tissue guided regeneration material from Gore-Tex.

Two swine will be euthanatized at one month, two months, four months, six months, eight months and twelve months to obtain specimens for histological studies.

Barium sulfate mixed with heparinized formalin will be infused after euthanasia to make neovascularization in the bone grafts identifiable radiographically.

Each bone grafts site will be physically measured for evidence of bone resorption or growth, and the measurements will be compared with the dimensions of the bone grafts measured at time of initial placement.

The titanium implants are of fixed length and will serve as markers for loss on maintenance of the bone graft heights as well as the above physical measurements.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: There have been eleven subjects entered with two having adverse reactions. Two of the swine developed severe post surgical infections that necessitated earlier than planned necropsies, and two of the swine developed severe post surgical infections that required multiple anesthesia events for incision and drainage and debridement. The source of the infections was found to be from improper processing to the freeze-dried allogeneic bone grafts, and this has since been corrected. Two more animals were purchased to keep the number of specimens adequate for this study. Surgeries for the remaining six miniature swine have been postponed until October 1994 to allow for a comprehensive review and correction of the source of morbidity to the four infected swine. The estimated completion date has changed from Jan 94 to Jul 96.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/06 STATUS: Completed FY94

TITLE: The effect of surface preparation on the solder joint strength of two dental alloys

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Donn A. Grimes

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Solder Joint Strength

Study Objective: The objective of this research is to determine if there is a surface preparation technique that will encourage better wetting by the molten solder and thus form a stronger and more reliable solder joint.

Technical Approach: Specimens from each dental alloy will be fabricated using the lost wax casting technique and acrylic resin and wax patterns IAW ISO 9333. The specimens from each alloy will be arbitrarily divided into one of three groups by an un-informed and disinterested person. All specimens will be given an identification number for future reference.

The specimens within a group will be individually sectioned, followed by the specific surface preparation for that group and then soldered with the manufactures recommended solder and flux. The gap distance will be 0.2 mm (IAW ISO 9333). All soldering will be performed by one person after sufficient practice and training to ensure a standardized technique. Five specimens of each group will be soldered at a time. The soldering will proceed from a group of one alloy to a different group in the other alloy until all specimens have been soldered.

All specimens will be subjected to four simulated bakes in the porcelain furnace in order to simulate the oxidizing, opaque, and body bakes which are common to metal-ceramic procedures. This important step is necessary to negate the effects of internal stresses from casting and to standardize the effects of possible age hardening. Five specimens from each of the six groups will then be selected by a un-informed and disinterested person for SEM evaluation of the solder/parent metal alloy interface. The remaining thirty specimens from each group wil undergo tensile stress testing.

The SEM analysis will be characterized by alloy group. The data from the tensile stress testing will be compiled and submitted for statistical analysis to determine if a significant difference exists between the groups.

Progress: This study has been completed.

Abstract: Connector surfaces of a noble alloy (high palladium-gold) were prepared using one of three techniques: (1) aluminum oxide air abrasion, (2) rubber polishing wheel, and (3) fine garnet abrasive disk. All connectors were subjected to preceramic soldering (presoldering) using a standard technique and simulated porcelain firing. Evaluations included SEM analysis of the parent alloy and solder interface, tensile strength tests, and fracture mode analysis. No statistical differences (one-way ANOVA, $p < 0.05$) were found between the three surface preparation techniques. A power analysis (effect size 0.72, power 0.08) was performed to determine the probability of detecting a difference if one existed. The low power suggests that a much larger sample size (n=610) per technique would be required to say for certain that there are no differences between the groups. Evaluation of the parent alloy and solder interface, and the mode of fracture support the findings that there are no differences between the three techniques.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/01 STATUS: Completed FY94

TITLE: The effects of temporary cements on provisional restorations

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 93 ESTIMATED COMPLETION DATE: Feb 94

PRINCIPAL INVESTIGATOR: MAJ Andre K. Kim

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Temporary Cements

Study Objective: The objective of investigation is to determine the softening effects of four temporary cements under two different conditions. The results should show an ideal combination of provisional resin and temporary cement that will withstand the prolonged treatment time required in a military environment.

Technical Approach: The purpose of the investigation is to evaluate four different temporary cements against four different provisional resins.

Temporary Cements:

1. Temp-Bond - most often used temporary cement
2. Temrex - 95% eugenol in liquid portion of the cement - will be used to compare to Temp-Bond to investigate if the concentration of eugenol influences the investigation
3. Temp-Bond NE - counterpart of Temp-Bond, but free of eugenol
4. Nogenol - a temporary cement without eugenol

Provisional Resins:

1. Alike - polymethyl methacrylate
2. Jet - polymethyl methacrylate
3. Snap - polyethyl methacrylate
4. Protemp - composite material

1. Resin disks will be made using stainless rings.
2. The resin ring will be exposed to tested temporary cements, in between glass slabs - similar to Rosenstiel and Gegauff's study.
3. The glass slabs containing resin rings that are exposed to temporary cements will be under 100% humidity (group A) and submerged in water (group B). The control group (group C) will be free of cements under both conditions. The duration for tests will involve up to a 2 week exposure of the discs.
4. The temporary cements will be removed from the resin disks.
5. The surface hardness will be measured using Barcol Tester.
   Five readings will be done on each resin disk, and each group will have eight disks.

Progress: The study has been completed.

Abstract:Eugenol has been shown to have many adverse effects on the physical properties of resin. It softens, decreases transverse bend strength and surface hardness, interferes with polymerization of composite resin and discolors the resin. The study compared the effects of eugenol-containing and non eugenol-containing temporary cements on surface hardness of provisional resins under two different environments (100% humidity, and immersed in sterile water). The examined temporary cements were Nogenol, Temp-Bond, NE and Temrex. Four Provisional resins compared were Alike, Jet, Protemp II and Snap. Resin disks that were not subjected to the

cements used as a control group. Each group of resins disks was subjected to each examined temporary cement for 14 days. A hand-held hardness tester (The Impressor) was used to measure the surface hardness of resin samples. The results showed statistically significant differences between two different conditions, among resins and the cements, and significant interactions between resin and cement tested ($p<0.001$). Each provisional resin had a different inherent surface hardness and each appeared to have different response to temporary cements. Three of tested provisional resins showed some decrease in surface hardness by all tested cements whether the cement contained the eugenol or not. The Protemp II had the highest surface hardness and it did not appear to be affected by any of the cements tested. There was no significant difference between resin samples subjected to Temp-Bond (eugenol-containing cement) and Temp-Bond NE (non eugenol-containing). The results suggests that the softening effect of eugenol in temporary cement may not be as great in some provisional resins as it was previously thought.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/33A STATUS: Ongoing

TITLE: Autologous Pericranium for Temporomandibular Joint Disc Replacement in Sheep

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jun 93 ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: LTC(P) John C. Mitchell

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MG Donovan, NC Dickerson

KEY WORDS: TMJ, Discectomy

Study Objective: (1) Determine the success of autologous pericranium as a temporomandibular joint disc replacement tissue utilizing histological assessments of the morphological changes of the pericranium at timed intervals.

(2) Compare condylar morphological changes in temporomandibular joints repaired with pericranial grafts and joints in which unrepaired discectomies are performed.

Technical Approach: (1) Fifteen domestic sheep will be used for this study. A control for a normal temporomandibular joint disc and condyle have been previously studied histologically.

(2) Under general anesthesia, each of the fifteen sheep will have autologous pericranium harvested via a biocoronal flap. An incision over the zygomatic arch and glenoid fossa will give access to the temporomandibular joint space. The TMJ discs will be excised bilaterally and the pericranium sutured to the anterior and posterior stumps of the TMJ disc attachments with non resorbable sutures unilaterally. The other temporomandibular joint will go unrepaired following its discectomy.

(3) Three sheep will be euthanatized at one month, two months, four months, six months, and ten months to obtain specimens for histological studies.

(4) The pericranium from each joint site will be studied for histological changes and fibrous adhesions.

(5) The condyles of each animal will be studied to assess any changes as a result of the autologous pericranium TMJ disc replacement. These will be evaluated radiographically and by histological sections.

Progress: Preliminary results of necropsies and gross and histological examinations of the operated sheep temporomandibular joints have been some what equivocal. Two animals are being held for a 12 month follow-up as long term osteolytic changes are suspected in this study that have not been seen in the early samples. Arrangements have been coordinated with Dr. Harris, Chief, Bioresearch Lab, to maintain these two sheep for 12 months. There has been a change of principal investigator from LTC Roland G. Gustafson to LTC(P) John C. Mitchell.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/26A STATUS: Ongoing

TITLE: Pericranium as a Tissue Barrier in Mandibular Reconstruction in Sheep (Ovis aries)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 94 ESTIMATED COMPLETION DATE: Jul 95

PRINCIPAL INVESTIGATOR: CPT Timothy C. Snyder

DEPARTMENT: DENTAC FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JC Mitchell, MG Donovan, NC Dickerson

KEY WORDS: Pericranium. Mandibular Reconstruction

Study Objective: (1) Determine the viability of pericranium used as a free graft over transoral mandibular reconstruction sites.

(2) Compare the incidence of infection, wound breakdown, and retention of autologous corticocancellous iliac bone grafts placed trans orally in mandibular defects closed primarily with and without the use of autologous pericranium.

Technical Approach: (1) Eight Rambouillet sheep will be used for this study. Each animal will serve as its own control.

(2) Under general anesthesia, each of the eight sheep will have autologous corticocancellous iliac bone grafts harvested via b

Progress: The surgery start date was October 1994. There have been 8 subjects entered with no adverse reactions noted to date. The estimated completion date has been changed from Sep 94 to Jul 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/41 STATUS: Completed FY94

TITLE: Blood pressure control during scheduled conversion of nifedipine XL to amlodipine

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Jeffrey R. Abrams

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L McConnell

KEY WORDS: Amlodipine, Hypertension

Study Objective: (1) To determine if adequate blood pressure control can be maintained during a scheduled conversion of nifedipine XL to amlodipine (2) To determine if side effects are less common with amlodipine (3) To determine if adequate control of hypertension is less expensive with amlodipine.

Technical Approach: The study will be a prospective, open label trial that utilizes each patient as his or her own control. The incidence of adverse effects and adequate control of blood pressure will be the main parameters that are monitored.

Progress: The study has been completed. Twenty-four patients were entered in the study and three withdrew. No adverse reactions were noted.

Abstract: Amlodipine besylate is a unique dihydropyridine calcium channel blocker that has a long half-life (>50 hr). Due to formulary changes, convenience, cost, or side effects, hypertensive patients previously controlled on nifedipine XL may be switched to amlodipine. However, only limited literature is available comparing the potency of these two agents. To simplify the conversion process, a programmed conversion schedule was devised and then evaluated in a group of patients with moderate to severe hypertension. Twenty-four patients with stable blood pressures (BP's) who were using nifedipine XL were enrolled in a prospective study. Baseline BP's were obtained one week apart prior to switching to amlodipine as per the following conversion schedule: nifedipine XL 30 or 60 mg = amlodipine 5 mg, nifedipine XL 90 or 120 mg = amlodipine 10 mg. BP's were then monitored for 7 weeks. Twenty-one patients completed the study. Two patients withdrew due to anxiety about being in a study. One patient was unable to report for the weekly BP's. The group's average age was 57; 55% were male. Comorbid illnesses included: diabetes (28%), atherosclerotic heart disease (9%), renal transplant (24%), and chronic renal failure (62%). The average calculated creatinine clearance was 50 ml/min. At baseline, the BP was 151 + 3/82 + 2 mmHg at a cost of $2.17 per day. The BP rose slowly during the first 3 weeks of amlodipine therapy consistent with the drug's prolonged half-life. However, 4 weeks after beginning amlodipine, the BP was 148 + 5/80 + 3 mmHg at a cost of $1.54 per day. (BP + SE, p-values 0.27 for systolic and 0.24 for diastolic pressures) Nifedipine XL and amlodipine appear equally efficacious with the present conversion schedule. Therapy with amlodipine is less expensive and may be more convenient since patients do not require the split dosing schedule that is often used at the higher doses of nifedipine XL.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/24 STATUS: Ongoing

TITLE: PCR Detection of Hepatitis C Virus in Serum and Dialysate of Hemodialysis Patients

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 94 ESTIMATED COMPLETION DATE: Jul 94

PRINCIPAL INVESTIGATOR: MAJ Jeffrey Abrams

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: PCR, Hepatitis C, Dialysis

Study Objective: To evaluate hemodialysis patients who are HCV antibody positive, by second generation ELISA testing, for evidence of viremia in serum by PCR and determine if contamination of the dialysate has occurred again with the use of PCR.

Technical Approach: Enroll hemodialysis patients who have been screened by hepatitis serologies and have been found to be HCV antibody positive by a second generation ELISA test. Obtain demographic data (see attached data form) from medical records and patient. Obtain serum and pre- and post-dialysis dialysate samples from these patients and perform PCR to identify HCV RNA. Detection of HCV RNA has been shown to be inhibited by heparinized blood (49). Therefore, serum and dialysate samples are to be collected in EDTA tubes and non-heparinized dialysis treatments will be attempted. Prior to performing PCR on the samples heparinase will be administered to dialysate samples to eliminate interference by heparin. In addition to the PCR the following blood tests will be performed: Biliary panel and Hepatitis B serologies, if not performed previously. For those dialysate samples that are positive by PCR, a repeat study will be performed and a sterilant will be used on the dialysis equipment and PCR repeated on the dialysate to see if sterilant eliminated viral mRNA.

Progress: Serum from two EIA-positive patients were tested by RT-PCR for HCV. Both were negative RT-PCR. There has been a change of principal investigator from CPT Robert Wolfgang to MAJ Jeffrey Abrams.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/09 STATUS: Terminated FY94

TITLE: Landmark Investigation of Felbamate in Epilepsy

MONITOR (applicable for projects reviewed semi-annually): COL Pilar Cortez

START DATE: Dec 93 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: MAJ Jonathan Braiman

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Braiman

KEY WORDS: Felbamate, Epilepsy

Study Objectives: Evaluation of changes in patient outcome in an adult population of epileptics when felbamate is substituted for an antiepileptic drug (AED). Outcomes will include changes in pre-study side-effects and changes in seizure frequency.

Technical Approach: An open label, multicenter trial of seven weeks duration. It will include a three week titration phase and four week treatment phase. The use of felbamate and pre-study AED's will be in accordance with the indications and dosing guidelines of the product labeling.

Four patient visits will take place during the seven week study. No diagnostic tests or blood level determinations will be required during the study.

Amended Feb 94: Funding for felbamate will be provided by DCI and reimbursement will be requested at a later date from Wallace Laboratories through Jackson Foundation.

Progress: Semi-Annual Review (Apr 94): Four subjects have successfully completed the study and have benefited from the medicine with fewer seizures and/or side effects. These patients continue on the medication.
One patient withdrew from the protocol after several weeks because of uncomfortable side effects (mild anorexia, paresthesia along both forearms) and has gone back to her prior therapeutic regimen with resolution of the paresthesia. A sixth patient is just beginning the protocol. Annual Review: This study was terminated in July. A total of six subjects were entered, but two withdrew due to uncomfortable side effects (anorexia, paresthesia along both forearms, vomiting). Carter-Walla aborted the study and issued a statement concerning the development of an unexpectedly high risk of aplastic anemia in patients who were part of the study. One patient who derived excellent benefits from Felbamate not previously experienced on multiple anticonvulsant, has decided to continue taking the medication, fully appreciative of the recent information. Data collection will be completed six months from the completion date of October 1994. There has been a change of principal investigator from MAJ Cornelius C. Maher to MAJ Jonathan Braiman.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/05 STATUS: Ongoing

TITLE: The Prevalence and Severity of Band-Keratopathy in Patients with Primary Hyperparathyroidism

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 93 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: CPT Luis M. Irizarry

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): KJ Simcic, DP Mong, WF Davitt

KEY WORDS: Primary Hyperparathyroidism, Band-Keratopathy

Study Objective: To assess the frequency and severity of BK in patients with PHP. If the frequency of bk is significant in these patients, possible correlations with the duration and or severity of the php will be examined.

Technical Approach: Single center, prospective, single blind case control study.

Progress: There has been 30 subjects entered with no noted adverse reactions. We have now completed eye exams on 22 patients with primary hyperparathyroidism (with an average duration of 8-10 years) and on 8 control patients. We would like to recruit and test a few more control patients before ending the study. The estimated completion date has been changed from June 1994 to March 1995. Although the study is negative thus far, we feel that our results are still significant. It appears that patients with primary hyperparathyroidism can be permitted to live with their disease untreated for at least 8 -10 years without significant risk of band-keratopathy.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/32 STATUS: Ongoing

TITLE: Talc Insufflation vs. Minocycline in a Randomized Double Blind Prospective Trial of Intrapleural Therapy for Recurrent Malignant Pleural Effusions Via Thoracoscopic Guidance

MONITOR (applicable for projects reviewed semi-annually): LTC James Wallingford

START DATE: May 94 ESTIMATED COMPLETION DATE: Jun 97

PRINCIPAL INVESTIGATOR: MAJ Lynn M. Keenan

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JL Cadiz, SP Hetz, B Hammacker, P Stanley, GR Ripple

KEY WORDS: Talc vs. Minocycline

Study Objective: To determine the efficacy of minocycline vs. talc insufflation for sclerosis of malignant pleural effusions via thoracoscopic guidance.

Technical Approach: This study follows standard of care for patients with pleural effusion who are scheduled for thoracoscopic pleurodesis. The only deviation involves use of minocycline in the experimental group. We will follow patients from diagnosis through followup.

1)The patient with clinically suspected recurrent free flowing malignant pleural effusion by pleural fluid cytology or pleural biopsy will be identified.

2)The patient will undergo chest X-rays, which should show freely flowing pleural fluid or loculated fluid and confirming the lack of mediastinal shift.

3)If the patient meets eligibility criteria, informed consent will be obtained and the patient will be enrolled into the study.

4)A data sheet (see Appendix I) will be kept recording laboratory data, ECOG performance status, and chest radiograph results as well as demographic information: age, sex, institution, diagnosis, stage of disease, type of chemotherapy received, side effects to the sclerosant including: pain, fever, hypotension, allergic reaction, rash (maculopapular or erythematous), fatigue, anorexia, nausea, vomiting, diarrhea, elevated liver function tests, anemia, neutropenia, and elevated blood urea nitrogen or creatinine.

5)Sclerotherapy procedure:

(a) IV sedation with Versed and Morphine sulfate titrated to drowsiness and slurred speech.

(b) After the patient is placed in the lateral decubitus position and the chest is prepped and draped, a 10 mm thoracoport will be introduced into the pleural cavity under local anesthesia. Any loculated fluid will be aspirated and adhesions gently taken down. Then, the randomly selected sclerosant (talc<3 g vs. minocycline 300 mg) will be sprayed into the pleural cavity coating both the visceral and parietal pleura.

(c) After 20 minutes, a chest tube will be inserted and placed on suction, re-expanding the lung.

(d) Suction will be maintained for at least 24 hours and until pleural drainage is less than 150 ml/day. Then the chest tube will be removed.

(e) From the time the sclerosant is injected the patient will receive 650 mg of Tylenol PO every four hours for a total of 48 hours.

6) Chest radiographs will be obtained at 72 hours to assess for recurrence of the effusion after the sclerosis. If the fluid reaccumulates more than 50% of the original volume after sclerosis, the patient will be considered a treatment failure and considered for either no further treatment or surgery.

7) The following labs will be obtained at 24 and 48 hours for monitoring of side effects: complete blood count, liver function tests, blood urea nitrogen and creatinine.

8) The investigators will monitor for the side effects mentioned on the flow sheet during the first 48 hours after the sclerosis has been completed.

9) Assuming the sclerosis is initially successful, chest radiographs will be obtained at 7 days, 14 days, 30 days, 60 days and 90 days to assess for response. Response rates will be defined in the following manner:

(a) Complete response: No fluid present on chest radiograph.

(b) Partial response: asymptomatic pleural fluid equal to less than 50% of the original width at mid thorax measured on the lateral decubitus film.

(c) Treatment failure: recurrence of the pleural effusion greater than 50% of the original width at mid thorax measured on the lateral decubitus film, a loculated pleural effusion which is 50% of its original volume on PA and lateral roentgenograms or a recurrent symptomatic effusion of any size.

(d) All chest roentgenograms enrolled in the study at WBAMC will be read by the same observer, Dr. Ripple.

Progress: There have been 3 subjects entered with no noted adverse reactions. The estimated completion date has changed from May 94 to Jun 97.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/33 STATUS: Ongoing

TITLE: Comparison of a High Resolution Computed Tomography Technique and Fiberoptic Bronchoscopy in the Evaluation of Hemoptysis

MONITOR (applicable for projects reviewed semi-annually): LTC Gary Ripple

START DATE: May 94 ESTIMATED COMPLETION DATE: May 96

PRINCIPAL INVESTIGATOR: MAJ Lynn M. Keenan

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JL Wallingford, R Gore, MC Hodges

KEY WORDS: Tomography, Bronchoscopy, Hemoptysis

Study Objective: We propose a collaborative study to examine the role of combining HRCT with fiberoptic bronchoscopy in the evaluation of hemoptysis. The standard of care presently for hemoptysis of unknown etiology involves a history, physical examination, screening labs, PA and lateral CXR, fiberoptic bronchoscopy if the diagnosis is not readily explainable, and CT of the chest if predicated by the chest roentgenogram.

Technical Approach: Study patients will receive a standardized initial work-up to include history and physical examination, screening labs, and PA and lateral chest roentgenograms. Demographic data to include age, sex, tobacco history, and frequency an

Progress: There have been 6 subjects entered with no noted adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/54 STATUS: Ongoing

TITLE: Prospective Evaluation of Coccidioidomycosis in Human Immunodeficiency Virus-Infected Individuals Living in an Endemic Area

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 1991 ESTIMATED COMPLETION DATE: Aug 2001

PRINCIPAL INVESTIGATOR: Lynn McNicol

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): N Aronson

KEY WORDS: Coccidioidomycosis, Human Immunodeficiency Virus

Study Objective: To demonstrate whether coccidiomycosis seen in HIV patients is reactivation disease or represents acute infection in an immunocompromised host. To assess the early predictive value for active coccidioidomycosis of the spherulin skin test, coccidioides complement fixation and immunodiffusion antibody studies and coccidioides antigen ELISA in the HIV infected population.

Technical Approach: The is a prospective descriptive study. Subjects will be obtained from individuals participating in the HIV natural history study 86-49 (non-active duty) and HIV infected active duty soldiers who are followed in the WBAMC Infectious Disease Clinic per AR 600-110. Completion date is dependent on number of patients enrolled and severity of their immunologic compromise. Estimated study duration is 5 years.

On entry, a complete geographic history will be obtained to assess travel to Cocci endemic regions (West Texas, Arizona, San Joaquin Valley in California). On entry and every 6 months thereafter, delayed hypersensitivity skin testing will be performed IAW DOD HIV staging. In addition, spherulin 1:100 (Berkeley Biologics) will be included in the battery which is already usual practice in cocci endemic regions. Chest radiograph will be obtained on entry and every 12 months which is current clinical practice during HIV staging. On entry and every 6 months, the following blood tests will be ordered: T cell subset by flow cytometry, quantitative immunoglobulins and STEP, complement fixation Coccidioides antibodies (sent to Dr. appagianis' laboratory at UC, Davis), Coccidioidal precipitins (sent to FSH, TX), serum for coccidioidal antigen (research test) - will be frozen at -70o F initially. On entry and every 6 months, weight will be recorded. On entry and at every subsequent staging, patient will be clinically evaluated by history and physical examination to assess for presence of active coccidioidomycosis.

Progress: Amended April 1994: Completion date has been extended to 2001. Modifications detailed above are included in the amendment.

Annual Report (Oct 94): Seventy-five individuals initially signed consents for this study. Of these seventy-five, fourte

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/36 STATUS: Ongoing

TITLE: Effect of Heart Disease on the Hemodynamic Response to Supine Upper Extremity Exercise

MONITOR (applicable for projects reviewed semi-annually): COL Harry Davis

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Mar 93

PRINCIPAL INVESTIGATOR: CPT Timothy W. Martin

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Belbel, L Brenner

KEY WORDS: Exercise, Hemodynamics, Cardiac Catheterization

Study Objective: Characterize and compare the hemodynamic response to supine upper exercise in patients with and without heart disease.

Technical Approach: Patients who require heart catheterization and do not have exclusion criteria will be identified and counselled by cardiology staff. Consenting patients will be brought to the catheterization laboratory in a fasting, mildly sedated state. From the femoral approach, a Swan Ganz catheter will be advanced to the right heart and a pigtail catheter will be advanced to the left heart. Resting pressure and flow measurements and blood samples will be obtained. The patient will then perform five to eight minutes of supine arm cycle exercise, during which rest measurements will be repeated. Based on the results of rest measurements, angiography, and other clinical information, patients will be categorized as normal or as having coronary artery disease, cardiomyopathy, or valvular heart disease. The response to supine upper extremity exercise will be compared among the groups.

Progress: Semi-Annual Review (Apr 94): No response received from investigator.

Annual Review: No response from investigator for FY 94 annual report.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/16 STATUS: Ongoing

TITLE: Cardiopulmonary Response to Upright Exercise in Patients with Asymptomatic Valvular Aortic Stenosis and Patients with Aortic Valve Prostheses

MONITOR (applicable for projects reviewed semi-annually): COL Idelle Weisman

START DATE: Feb 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Timothy W. Martin

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Belbel

KEY WORDS: Upright Exercise, Valvular Aortic Stenosis, Aortic Valve Prostheses

Study Objective: To determine the effect of valvular aortic stenosis and aortic valve replacement on cardiopulmonary exercise performance and the relationship between ECHO\Doppler measurements and cardiopulmonary performance in patients with valvular aortic stenosis and aortic valve prostheses.

Technical Approach: A total of 75 patients (ages 18-75) will be included in the study (25 with aortic stenosis, 25 with aortic valve prostheses, and 25 controls). Patients will undergo upright cycle exercise, 20 W/min increments, symptom-limited, followed by cool-down exercise with continuous monitoring of O2 consumption, CO2 production, tidal volume, anaerobic threshold, respiratory rate, heart rate, power, amd blood pressure. Patients will be monitored for 10 minutes following the exercise test.

Progress: Semi-Annual Review (Apr 94): No response was received from the investigator.
Annual Review: No response received from investigator for FY 94 annual report.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 76/33 STATUS: Ongoing

TITLE: Diagnostic Adrenal Scanning with 131I (NP59)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 76 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Albert J. Moreno

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Adrenal Scanning

Study Objective: To determine the usefulness of 131I-NP59 in scanning of the adrenal glands. This agent will be used (1) as a screening test for detection of primary aldosterone tumor, Cushing's disease, adrenal cortical adenoma, or pheochromocytoma; (2) to image adrenals in patients who require adrenal venography and are allergic to contrast media; (3) to detect unilateral adrenocortical hypofunction - calcification, metastatic carcinoma, post-venography infarction, etc.; (4) to detect functioning adrenal remnant after adrenalectomy for Cushing's syndrome; (5) to aid in assessment of adrenocortical function in patients who have been on adrenocortical steroid therapy.

Technical Approach: Patients with clinical evidence of adrenal disease will be thoroughly evaluated by an endocrinologist. Following intravenous administration of 131I-NP59, adrenal scanning will be performed after 7-10 days. The material will be obtained from the Nuclear Pharmacy, University of Michigan. The WBAMC radiopharmacist will perform sterility and pyrogenicity tests on the radiochemical to ensure that radiopharmaceutical standards are met prior to injection

NOTE: Project was erroneously terminated in Oct 84. Project reactivated in Sep 92 and folder was reconstituted to include required documentation.

Progress: Twelve patients have been studied since this protocol was approved. No adverse effects noted.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/57 STATUS: Terminated FY 94

TITLE: NSABP C-05: A Clinical Trial to Assess the Relative Efficacy of 5-FU + Leucovorin with or without Interferon Alfa-2a in Patients with Dukes' B and C Carcinoma of the Colon

MONITOR (applicable for projects reviewed semi-annually): MAJ Jay Carlson

START DATE: Sep 92 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ Michael E. Nash

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

KEY WORDS: Dukes' B & C Carcinoma

Study Objective: This study will evaluate the relative effectiveness of 5-FU plus Leucovorin with and without alfa interferon in prolonging disease free and overall survival in patients who have undergone standard curative resection of Dukes' B and C carcinoma of the colon.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients entered to date. Protocol is ongoing.
Annual Review: This study has been terminated by principal investigator's choice.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/36 STATUS: Completed FY93

TITLE: The Effect of Meal Consumption Before Radionuclide Ventriculography

MONITOR (applicable for projects reviewed semi-annually): LTC Algeo

START DATE: Jul 93 ESTIMATED COMPLETION DATE: Apr 94

PRINCIPAL INVESTIGATOR: LTC Elmer J. Pacheco

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Moreno, G Turnbull, M Brodbeck, D Hokanson

KEY WORDS: Meal Radionuclide Ventriculography

Study Objective: To determine the effect of a standardized meal on the resting LVEF in patients with a normal LVEF.

Technical Approach: A retrospective and prospective study in which patients with a known normal LVEF derived through a MUGA performed at our institution and during a fasting state, will be asked to undergo a repeat study 45 min after the ingestion of a standardized meal totalling 700 cal, consisting of 50% carbohydrates, 30% fat, and 20% protein. This meal will consist of 4 oz orange juice, 8 oz 2% milk, 2 pieces of toast, 2 boiled eggs, 2 slices of bacon, 1 cup of coffee with sugar and non-dairy cream, and 1 banana.

Progress: Semi-Annual Review (Apr 94): Abstract presented to Society of Nuclear Medicine Southwest Chapter 39th Annual Meeting, 7-10 April 1994:
We are prospectively evaluating the effect of meal consumption on left ventricular ejection fraction (LVEF) in normal adult volunteers. The purpose of the study is to validate previous results found in patients with stable congestive heart failure (CHF) who had an increase in the LVEF after eating a standardized meal. Twelve patients have so far completed our study, consisting of LVEF determinations during the fasting state, and 45 minutes after having consumed a 700 calorie standardized breakfast. The mean fasting LVEF (FLVEF) was 62.5 ± 5.3% , and the mean post-prandial LVEF (PPLVEF) was 67.1 ± 5.3%. The mean increase in LVEF observed in 9/12 subjects was 7.1 ± 4.0%. This is statistically significant. Consumption of a meal prior to performing Radionuclide Ventriculography will significantly increase the LVEF, in both normal volunteers and in patients with CHF.
After submission of this abstract, an additional 13 patients were enrolled, results support conclusions detailed in the abstract.
Of the 25 patients enrolled, 5 withdrew due to scheduling conflicts.Study has been completed.
Annual Review: Study reported as completed upon semi-annual review in April 1994.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/53 STATUS: Terminated FY 94

TITLE: Phase II Study of Interferon-Modulated Indium-111-Labeled b72.3 Monoclonal Antibody (MoAb) Scintigraphy in the Staging and Follow-Up of Breast Cancer Patients of Poor Prognosis

MONITOR (applicable for projects reviewed semi-annually): MAJ Jennifer Cadiz

START DATE: Nov 1993 ESTIMATED COMPLETION DATE: Oct 2000

PRINCIPAL INVESTIGATOR: LTC Elmer J. Pacheco

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Moreno, W Sippo, S Hetz, TH Nguyen, ME Nash, GG Turnbull, G Morgan

KEY WORDS: Breast Cancer, Scintigraphy

Study Objective: The use of human leukocyte interferon-alpha (HuIFN-a)in this study would attempt to enhance the expression of a tumor-associated antigen (TAG-72) in breast cancer patients of poor prognosis. The sensitivity and specificity of Indium-111-labeled B72.3 MoAb against TAG-72 in this subset of patients will be compared to conventional bone scintigraphy during their initial staging and follow-up. An analysis of the poor prognostic factors (i.e. Aneuploid DNA content, high S-phase, high Ki-67 growth fraction, negative ER/PR status, low pS2, high EGF, high HER-2neu, high Cathepsin D level, and low p53 expression) will be performed so as to document their importance in the prediction of survival in this set of patients, as well as discerning which combination of these factors will more accurately predict outcome.

The Modified Scarff-Bloom-Richardson system will be compared to nuclear grading, with and without mitotic count in the histopathological assessment of the obtained tissues. Their effectiveness in predicting relapse will be defined.

Technical Approach: Details are too lengthy to list here. Protocol is on file in Department of Clinical Investigation.

Progress: Semi-Annual Review (Apr 94): The study has not yet begun. Investigators are awaiting notification concerning grant funding.
Annual Review: Protocol has been terminate due to disapproval of Jackson Foundation grant.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/49 STATUS: Ongoing

TITLE: The Natural History of HTLV-III Infection and Disease in a US Military Population

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 86 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LB McNicol

KEY WORDS: HIV Natural History

Study Objective: Study the epidemiology of HTLV-III infection in active duty and retired military personnel and their dependents.

Technical Approach: Standard evaluation will be routine medical evaluation, immunological evaluation, laboratory tests, tests for opportunistic infections, HTLV-III viral cultures on body fluids and organs whenever possible. Completion of HTLV-III clinical evaluation form. HTLV-III tests. Counselling, education, and referral of contacts. Follow-up of individuals in the study. Data analysis: disease progression will be studied, as defined by Walter Reed Staging Classification. The effect of variables, including but not limited to age, sex, ethnic background, risk factors, length of infection, and simultaneous viral infections, will be studied.

Addendum: 12 Feb 90 - This protocol was amended to exclude active duty servicemembers. At the directive of the Secretary of the Army, all active duty HIV+ servicemembers are to be clinically staged periodically.

Progress:No response received from investigator for FY 94 annual report.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/67 STATUS: Terminated FY94

TITLE: Investigational Prophylactic Use of Zidovudine in Health Care Workers Sustaining a Deep Percutaneous Occupational Exposure to Human Immunodeficiency Virus

MONITOR (applicable for projects reviewed semi-annually): COL Preston Cannady

START DATE: Jul 89 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LB McNicol

KEY WORDS: AZT, Zidovudine, Needle Sticks

Study Objective: To offer a defined course of zidovudine to HIV negative health care workers within 5 days of a significant exposure to HIV. To assess the safety and tolerance of 200mg zidovudine given orally every 6 hours for 42 days in otherwise healthy persons.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled over the past year. Study is ongoing.
Annual Review: The protocol has been terminated due to the fact that early use of AZT in this setting has become standard practice.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/05 STATUS: Ongoing

TITLE: Active Immunization of Early HIV Infected Patients with Recombinant gp 160 HIV protein Phase II Study of Toxicity Immunotherapy, in vivo Immunoregulation and Clinical Efficacy

MONITOR (applicable for projects reviewed semi-annually): COL Preston Cannady

START DATE: Nov 90 ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): CE Davis (WRAIR), G Martin

KEY WORDS: Recombinant gp 160 HIV Protein, Immunotherapy

Study Objective: To conduct a Phase II trial of the recombinant HIV envelope glycoprotein gp160 candidate vaccine, in patients with early HIV infection (Walter Reed Stage I-II). Specific objectives include:
1) To continue to evaluate the immunogenicity and toxicity of this product;
2) To determine the parameters predictive of immunoresponsiveness; and
3) To determine the clinical efficacy of immunization with pg160 in the treatment of early HIV infection.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Addendum: Modifies eligibility criteria. Approved by Tri-Service HUC (26 Feb 91), WBAMC HUC/IRB (23 Apr 91) and WRAMC HUC.

Amendments: (1) Deleted recipe skin testing on Day 180 (typographical error); WBAMC IRB notified 16 Jul 91. (2) Day 210 tetanus immunization shifted to Day 240 and Day 210 visit deleted; WBAMC IRB notified 17 Aug 91. (3) Initiated Phase IIB; presented to IRB 21 Apr 92. (4) Booster vaccinations to be given at 2 month intervals; presented to IRB 21 Jul 92. (5) CHECK PROTOCOL.

Progress: Semi-Annual Review (Apr 94): No new patients have been enrolled. One patient withdrew due to his reluctance to come in for protocol visits since they interfered with his work schedule.
Annual Review: There are 9 patients active in this protocol. Two patients moved out of the area and are being followed by the San Antonio site. Of our 9 active patients, 1 reached primary end point in Mar 9; 2 reached secondary endpoint in Feb 93 and Dec 93; 1 patient died of pneumocystis pneumonia in Dec 93. Estimated completion date has changed from Nov 95 to Dec 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/65 STATUS: Ongoing

TITLE: Early Diagnosis of Tuberculosis Using Gene Amplification Techniques (GAT)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 92 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): WF Nauschuetz, HM Gelston, TJ Casey

KEY WORDS: Polymerase Chain Reaction, Tuberculosis

Study Objective: To compare gene amplification techniques with current culture methods in the diagnosis of tuberculosis.

Technical Approach: This protocol will consist of two phases. Phase I will be the validation phase and Phase II will be the prospective evaluation of clinical respiratory specimens. Sources will be consecutive specimens submitted to the WBAMC Mycobacteriology Lab as well as specimens from TB cases submitted to El Paso County Heath Laboratory.

Progress: To date, sputum specimens from El Paso County Health have been frozen. Approximately 30 of those specimens have been amplified under a different protocol. The estimated completion date has changed from Sep 94 to Jun 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/01 STATUS: Completed FY94

TITLE: Active Immunization of AZT-Treated HIV-infected Patients with Recombinant GP160 HIV Protein: Phase I/II Study of Immunogenicity Toxicity, and Effect in In Vivo Immunoregulation

MONITOR (applicable for projects reviewed semi-annually): MAJ William Raszka

START DATE: Feb 93 ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): CE Davis, D Slagle, LB McNicol, G Martin

KEY WORDS: Recombinant gp 160 HIV Protein, Iimmunotherapy

Study Objective: To conduct a Phase I/II feasibility trial of the recombinant HIV envelop glyprotein, gp160 candidate vaccine in patients who are HIV infected (Walter Reed Stage 1-5) and currently under treatment with AZT. Specific objectives include: 1)to evaluate the immunogenicity and toxicity of this product in HIV-infected individuals on AZT, and 2)to determine the parameters predictive of immune responsiveness.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Amendment (Jan 94): Details are lengthy. Copy on file at DCI.

Progress: Semi-Annual Review (Apr 94): Study has been completed. There were 5 patients from WBAMC who enrolled in the protocol. All completed this Phase I study with no adverse events reported.
Annual Review: Study reported as completed on semi-annual review, April 1994.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/10 STATUS: Terminated FY94

TITLE: A Randomized, Blinded Evaluation of Two Doses of Stavudine (d4T) in Severely Immunocompromised Patients with HIV Infection who have Failed or are Intolerant of Alternative Antiretroviral Therapy

MONITOR (applicable for projects reviewed semi-annually): MAJ William Raszka

START DATE: Nov 92 ESTIMATED COMPLETION DATE: Jul 94

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Hobratsch

KEY WORDS: Stavudine (d4T), HIV

Study Objective: The primary objective of this trial is to provided potentially effective antiretroviral therapy to patients with advanced HIV infection who are unable to take AZT or ddI. A second objective is to determine optimal dosing of this agent. Efficacy of this agent will be evaluated by measuring interval CD4 counts, interval p24 antigen levels, and measuring the time to onset of new AIDS-defining diagnoses.

Technical Approach: Sequential patients eligible for enrollment in this protocol will be randomized to receive one of two doses of d4T, determined by weight:
>60 kg.: 20 mg BID OR 40 mg BID
40-60 kg.: 15 mg BID OR 30 mg BID
<40 kg.: 10 mg BID OR 20 mg BID

Randomization will be performed by the manufacturer, and study drug will be shipped for each individual patient. Neither the principal investigator at WBAMC nor the patient will know the dosage supplied. Patients will complete a baseline assessment, will be monitored every two weeks for the first month, and then will be monitored monthly for as long as they continue on the study.

Addendum #1, Quarterly Safety Summary circulated to IRB 19 Jan 93

Amendment #2 presented to IRB 16 Feb 93; Adverse Event (WBAMC) was also presented at this meeting. Patient withdrawn from study and study drug returned to company. The complication was one of the commonly reported complications of this therapy.

Progress: Semi-Annual Review (Apr 94): One patient was enrolled by the previous principal investigator (DR. Slagle). Patient developed intolerable peripheral neuropathy and had to be discontinued from the drug. The FDA panel recently recommended approval of this drug; therefore, this protocol will likely be terminated soon.
Annual Review: d4T has been approved by FDA for use in HIV patients not tolerating AZT.
This occured in Jun 94, therefore this protocol has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/40A STATUS: Ongoing

TITLE: Comparison of Subcutaneous and Nebulized Trimethoprim-sulfamethoxazole in the Prophylaxis of Pneumocystis carinii Pneumonia (PCP) in Rats

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 93 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): RA Harris, TP Baker

KEY WORDS: Pneumocystis, Trimethoprim, Sulfamethoxazole

Study Objective: To determine if Pneumocystis pneumonia can be prophylaxed in rats using nebulized trimethoprim-sulfamethoxazole.

Technical Approach: This will be an animal experiment. Sixty Sprague Dawley rats will be divided into 3 groups of 20 rats. Group I will serve as control and receive nebulized D5W with 1% benzyl alcohol, the vehicle of trimethoporim-sulfamethoxazole. Group 2 will receive nebulized trimethoprim-sulfamethoxazole prophylaxis. Group 3 will receive twice weekly subcutaneous trimethoprim-sulfamethoxazole which has been shown to be 100% effective in preventing PCP in the rat.(25) Each rat will receive the same regimen of oral dexamethasone and tetracycline in the feed on Day 0 as per Hughes.(26) On Day 4 nebulization will be delivered in the same manner to all rats in Groups 1 and 2 using a micronebulizer(Bird Corporation, Palm Springs, Calif). During administration of nebulization the rats will be attached to a plethysmograph to monitor ventilation. Dose administered will be estimated by method as outlined by Girard.(9) Group 3 rats will also receive subcuatneous trimethoprim-sulfamethoxazole on Day 4. Prophylactic drugs will be administered subsequently weekly from Day 4. All rats will be inoculated intra-tracheally with 0.2 ml of a 2 X 106 trophozoite/ml solution on Day 6. Two sentinel rats from each group will be euthanized at weeks 2, 4, 5, 6 and 7 to monitor progress of infection. Plasma, lung and liver will be harvested from the sentinels and stored at -70oC to assay for drug levels. All euthanized sentinel rats and any rats dying during the experiment will be examined for evidence of PCP. PCP infection will be determined by special stains of lung tissue and described as either infected or not infected. Severity of infection will be graded according to the number of Pneumocystis cysts as per Girard et al.(25) The experiment will last 8 weeks. All rats will be euthanized at that time and assayed for evidence of Pneumocystis carinii infection. Serum liver function tests, BUN, creatinine and complete blood count will be done. Liver and lungs will be examined histologically for any evidence of toxicity. Survival will be expressed by Kaplan-Meier plot.

Progress: To date the material support (i.e. equipment) has not been available due to lack of funding. No progress has been made on this protocol.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/04 STATUS: Ongoing

TITLE: Molecular Epidemiologic Study of Methicillin Resistant Staphylococcus Aureus (MRSA) at William Beaumont Army Medical Center (WBAMC) in El Paso, TX

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Dec 93 ESTIMATED COMPLETION DATE: Aug 94

PRINCIPAL INVESTIGATOR: MAJ Wellington Sun

DEPARTMENT: Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Nauschuetz

KEY WORDS: MRSA, MECA

Study Objective: (1) To determine and compare MW's of RFLP's (Mec A & Tn 554) in MRSA isolates from different patients throughout WBAMC. Analysis will be used to try to determine if the MRSA arises from a common source or multiple sources.

(2) Epidemiologic chart review from these MRSA positive patients to help determine a common vs. multiple source. Also, we will try and identify a common vector in multiple point sources.

(3) Compare PCR data to antibiograms obtained in the microbiology laboratory.

(4) Compare and contrast data in number two and three.

(5) Hopefully the epidemiologic data derived from this study will improve methods of prevention in order to decrease the spread of MRSA at WBAMC.

Technical Approach: This project will be a single center (at WBAMC) retrospective study analyzing MRSA positive cultures obtained from routine microbiology specimens submitted. Staphylococcus aureus chromosomal DNA will be isolated, prepared and digested according to methods outlined by SaFigueiredo and Tomasz (8, 11). PCR probes for Mec A and Tn 554 will be used to identify these RFLP's on an electrophoretic gel to determine their respective MW's in comparison with a standard. Objectives are stated above.

Progress: The only progress made on this protocol is the collection of MRSA isolates (frozen). The gene amplification lab in DCI is focusing on TB. This protocol will be completed when personnel, both from DCI or DPALS, become available for the work. The estimated completion date has changed from Aug 94 to Dec 95. The original PI, Dr. Miller has left the institution and Dr. Wellington Sun has taken over study.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/40 STATUS: Ongoing

TITLE: RV84: Assessment of Risk Factors for HIV-1 Infection Among Active-Duty U.S. Military Personnel with Documented Recent HIV-Antibody Seroconversion - Phase II

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 94 ESTIMATED COMPLETION DATE: Jul 97

PRINCIPAL INVESTIGATOR: Patricia A. Frank, RN

DEPARTMENT: Med/Peds FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AR Morton

KEY WORDS:

Study Objective: To evaluate biological and behavioral determinants of HIV-1 Seroconversion by comparing medical, demographics, and behavioral histories of active duty personnel recently infected and/or diagnosed, with HIV-1 histories of individuals who have not seronverted over a similar period of time.

Technical Approach: The study will be conducted by military and civilian personnel (principal investigator, associate investigators and HIV-POC's) in the Army, Navy and Air Force. The sites where we plan to conduct the study have already agreed to participate in Phase II.

Enrolling subjects: A roster of seroconveter cases and matched controls will be provided to each HIV-POC. The roster will contain the name, rank, and unit assignment. Two male controls for each male case and three female controls for each female case should be recruited form the list of eligibles provided. It is the HIV-POC's responsibility to contact potential respondents and to invite these individuals to participate in the study. Recruitment will be conducted in accordance with the information provided on the consent agreement affidavit (enclosure #2). The importance of this study, along with the absolute safeguards to anonymity and confidentiality, should be stressed.

Upon enrollment, a study ID number will be assigned to each participant. This number will be entered into the computerized questionnaire and on the log of study participants (enclosure #5) with the corresponding case/control status of all participating individuals. HIP-POC will also be provided with the interval dates (i.e., last negative - first positive) for each seroconverter case. Interval dates for controls will be the same as their matched case. These dates should be entered into the computerized questionnaire of each participant. Subject's names or other identifiers must not appear on the log or the questionnaire. The log will be kept by the HIV-POC and will be mailed to WRAIR after interviews at the facility have been completed, so that case or control status can be determined for each completed questionnaire.

In addition to the log of study participants, another log (enclosure #6) of eligible cases and controls who decline to participate will be maintained by the HIV-POC. This log will allow for comparison of demographic information between case/control participants and nonparticipants to determine if those who volunteer for the study are different from those who do not, thus indicating the existence of potential study bias.

The HIV-POC must obtain signed consent before cases or controls are interviewed. Consent forms are to kept locally until the end of the study in 1997 and then will be turned over to the principal investigator.

The location and time schedule for interviewing must be flexible and designed for the ease and convenience of study participants. Individuals may wish to complete the computerized interview during duty hours (~0730-1630) or before/after duty hours.

Interviews: In order to minimize response bias, maximize confidentially, and standardize interview procedures, interviews will be conducted using a computer program modeled after the audio computer assisted self-interview system (ACASI) developed by Research Triangle Institute (RTI).(8) With this technology, the computer plays a recorded version of question and answer choices to the respondent over headphones. The

participants responds through the keyboard. The computer records the response and, based upon the answer, plays the next appropriate question. A laptop PC, programmed with the questionnaire in ACASI-type format, will be provided to each participating post. (A hard copy of the questionnaire for men and for women is presented at enclosure #7). Prior to beginning each interview, the HIV-POC will explain to the participant the nature of the study and the reason for the interview. Although the participant will have received this information previously from the HIV-POC and will have signed a consent form, the HIV-POC will again describe the study and stress that anonymity will be maintained at all times. The computerized interview will commence only after the HIV-POC is satisfied that the participant understands the procedures and has no questions.

The laptop computers will be stationed in a quiet and private room. Individuals directly associated with recruiting and assigning code numbers to study subjects will never have access to information obtained during the interviews of cases or controls. To ensure total confidentiality of the interview, the responses entered into the computer will be encrypted.

This process will make it impossible for anyone to examine the contents of the interview. The decryption key needed to translate the interview record into a usable format will be kept by the investigators at WRAIR.

Progress: Study has just started, therefore, no progress has been reported.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/36 STATUS: Ongoing

TITLE: Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT)

MONITOR (applicable for projects reviewed semi-annually): LTC Albert Moreno

START DATE: Aug 1994 ESTIMATED COMPLETION DATE: Aug 2001

PRINCIPAL INVESTIGATOR: CPT Andrew Quint

DEPARTMENT: Med/Peds FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Marcus

KEY WORDS: Hypertensive, Lipid Lowering

Study Objective: This study is a practice-based randomized, clinical trial of antihypertensive pharmacological treatment and, in a specific subset, cholesterol-lowering, in 40,000 high-risk hypertensive trial, including at least 55% African-Americans. The purpose of the antihypertensive trial component is to determine whether the combined incidence of fatal coronary heart disease (CHD) and non-fatal myocardial infarction differs between diuretlogic treatments -- a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an alpha adrenergic blocker (dixazosin). Because of the morbidity and mortality form cardiovascular diseases, and all-causes mortality, the antihypertensive trial component will not include a placebo or no-treatment control group. The purpose of the cholesterol-lowering trial hypercholesterolemic men and women aged 60 years and older with the 3-hydroxymethlglutaryl coenzyme A (HMG CoA) reductase inhibitor pravastatin will reduce all-cause mortality as compared to control group receiving "usual care".

Secondary objectives of both trial components are to compare the effects of their respective treatment regimens on cardiovascular mortality, major morbidity, health costs, and health-related quality of life. Additional secondary objectives of the antihypertensive trial are to compare the effects of alternative treatments on all-cause mortality and on major hypertension-related morbidity such as incidence and regression of left ventricular hypertrophy and progressive renal dysfunction. Additional secondary objectives of the lipid-lowering trial are to assess the long-term safety of HMG CoA reductase inhibitors in men and women aged 60 years and above (particularly with regard to mortality from non-cardiovascular causes), the effect of lipid-lowering on cancer incidence and mortality, and the effect of lipid-lowering on the combined incidence of fatal CHD and non-fatal myocardial infarction, especially in key subgroups (over age 65, women, African Americans, type II diabetics). Also, because this component of the trial will not be blinded, the incidence of myocardial infarction based on centrally coded changes in biennial study ECG will be looked at as an end point. The mean duration of the trial is expected to be 6.0 years, ranging from 5.0 years (for the last patient entered) to 7.5 years (for the first patient entered). To maximize statistical power for the primary hypothesis of the antihypertensive trial, i.e., the comparison of each alternative drug regimen to diuretic, 1.7 times as many patients will be assigned to its diuretic arm as to each of its other three arms (Table 1). It is anticipated that half of ALLHAT participants will be randomized to both trial components and that half will be randomized only to the antihypertensive trial component.

Technical Approach: ALLHAT will employ an organizational structure that differs markedly from the usual NHLBI-supported clinical trial. The trial will be performed by a large number (250-300) of practicing physician-investigators who will be compensated on a per capita basis for each patient seen according to a fixed payment schedule. Approximately 20% of study patients are expected to be recruited by the Department of Veterans Affairs (VA) hypertensive clinics.

Progress: Due to administrative delay involving IRB approval, no patients have yet been entered into study. We are awaiting final approval from ALLHAT, to be followed by arrival of study medications/supplies.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/39 STATUS: Ongoing

TITLE: Identifying Process Variations Via Risk-Adjusted Outcome

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 94 ESTIMATED COMPLETION DATE: June 95

PRINCIPAL INVESTIGATOR: MAJ Kathryn J. Dolter

DEPARTMENT: Medical Surgical CNS FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Pardi

KEY WORDS: Risk-Adjusted

Study Objective: A descriptive study designed to answer the following questions:

1) What are the differences between DOD medical center actual and predicted CABG mortality rates?
2) What is the hemodynamic knowledge and hemodynamic measurement and treatment practice of nurses and physicians caring for patients in DOD medical centers?
3) What is the relationship between hemodynamic knowledge and hemodynamic measurement and treatment practice of nurses and physicians caring for CABG patients in DOD medical centers?
4) Are there differences between nurse hemodynamic knowledge and hemodynamic measurement and treatment processes at DOD medical center with higher than expected mortality rates and DOD medical centers with lower than expected mortality rates?
5) What are the other unit and provider characteristics and processes of DOD medical centers with higher than expected CABG mortality rates and DOD medical centers with lower than expected CABG mortality rates?

Technical Approach: The purpose of this study is to assess the validity of using risk-adjusted mortality as a screening mechanism to identify variations in practice impacting on quality of care. It will utilize Department of Defense (DOD) risk-adjusted mortality to identify medical centers having the potential for post-operative CABG patient care process variations, and then assess these medical centers' processes, specifically focussing on post-operative hemodynamic practices of nurses and physicians caring for these patients.

The study will utilize a combination case control and exploratory descriptive design to assess input, process and outcome variables of the coronary artery bypass graft surgery (CABGS) patient care process. It will consist of two phases. Phase I will utilize a DOD database to risk-adjust DOD medical center CABGS mortality to identify medical centers having potential positive and negative CABGS patient care process variations. Twelve DOD medical centers perform this procedure. Phase II-A will involve in-depth review of patient care processes, specifically focussing on nurse and physician hemodynamic and organizational practices at 6 DOD medical centers: 2 with higher-than -expected CABGS mortality (the cases) and 2 with lower-than-expected and 2 with "median" CABGS mortality (the controls). A combination of observation of provider hemodynamic assessment and intervention practices and assessment of provider hemodynamic knowledge and organizational process via questionnaires will be utilized for the in-depth process reviews. Phase II-B will involve hemodynamic and organizational practice questionnaire administration to CABGS patient care personnel at the remaining 6 DOD medical centers which perform CABGS. Phase II-C will involve description of the CABGS care processes of DOD CABGS intensive care units through chart audit of all CABGS patients from the first 6 months of 1994 at the 6 DOD medical centers undergoing site visits. There are no safety concerns related to use of thesemethods. Descriptive statistics, logistic regression and correlation will be utilized to analyze the data.

Progress: Study has just begun, therefore, no progress was reported.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/66 STATUS: Ongoing

TITLE: Workload Management for Nurses in the Trauma Resuscitation Unit

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 93 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: CPT Virginia S. Hathaway

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Workload Management, Trauma Resuscitation

Study Objective: To develop an accurate tool to measure nursing workload in the Trauma Resuscitation Unit; to develop an accurate tool to measure trauma patient acuity in terms of nursing care hours; and to develop an accurate tool that can predict nurse staffing needs.

Technical Approach: This is a descriptive, exploratory study of all incoming trauma patients, "code 3" designated for the Trauma Unit beginning 1 October 1992 through 1 October 1993. We will use a specially designed Trauma Resuscitation Acuity Worksheet to calculate nursing care hours for each "code 3" trauma.

Progress: No subjects were entered this year. The pricipal investigator has changed form MAJ Susanne Clark to CPT Virginia S. Hathaway.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/11 STATUS: Completed FY94

TITLE: Intranasal Midazolam for Reduction of Preoperative Anxiety in Children

MONITOR (applicable for projects reviewed semi-annually): MAJ Steve Rubin

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: LTC Charles B. Hauser

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AR Brown, MA Lewis, DD Thompson, RA Packwood

KEY WORDS: Intranasal Midazolam Anxiety

Study Objective: The objectives of this study are to determine whether midazolam will reduce preoperative anxiety and decrease posthospitalization regressive behaviors in children. This study encompasses the primary factor presented in review of the literature, preoperative midazolam to decrease anxiety in children. But this study also incorporates the noted phenomenon of posthospitalization regression and correlates it with preoperative midazolam administration. This study provides a global demonstration of the effects of midazolam (preoperatively and posthospitalization) that has not yet been addressed in the literature. The ramifications of this study are imperative for care of the pediatric patient in locations beyond the operating room. This study opens the door for further research involving intranasal midazolam as a premedicant for painful and/or frightening procedures. It also allows an option for care providers that are not accustomed to caring for children and meeting their unique psychological needs.

Technical Approach: The research design for this study is experimental. The experimental group will receive the intranasal midazolam and the control group will receive intranasal physiologic saline. Subjects will be assigned to the control or experimental group based on a computer generated randomization table. This will be done by the pharmacy service. The investigators will not know what the subjects are receiving until the data analysis has taken place. A paired t-test will be used to statistically analyze the data obtained during this study. This test is used when obtaining two separate measurements from the same subjects.

Progress: Semi-Annual Review: Apr 94 - Six patients have been entered into the study. There are no adverse reactions to report. Estimation completion date is September 1994.
Annual Review: The study has been completed. There were 41 subjects entered with no noted adverse reactions. CPT RG Harmon was dropped from the protocol.

Abstract: The purposes of this experimental study were to (a) determine if children preoperatively medicated with intranasal midazolam, immediately prior to separation from a guardian(s) demonstrated less anxiety, (b) evaluate children treated with intranasal midazolam for demonstration of less posthospitalization regressive behavior than children given equivalent volumes of physiological normal saline. An experimental design was utilized to gather data with random sample methodology on 41 pediatric patients ages 18 months to 7 years. A preoperative behavior checklist, a pre-treatment preoperative anxiety assessment checklist and follow-up phone call 10 days posthospitalization re-assessing the anxiety assessment checklist were completed. Statistical analyses were performed utilizing paired students t-test, Mann-Whitney U test, chi-square analysis, and multiple linear regression analysis. A level of significance was set at $p < .05$. This study of the 21 pediatric patients who received intranasal midazolam and 20 who received intranasal physiologic saline, found lower levels of anxiety in the post-treatment group that received intranasal midazolam at $p < .01$. The group medicated preoperatively showed a statistically significant decrease in posthospitalization regressive behavior at the $p<.001$ level. This study provides a correlation between preoperative anxiety in children and the manifestation of posthospitalization\ regression.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/35 STATUS: Completed FY94

TITLE: Lack of Child Care Facilities at WBAMC: Impact on Nursing

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Sarah N. Lozano

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Child Care WBAMC

Study Objective: 1) Develop an index to measure level of child care problems.

2) Analyze and interpret collected data in order to evaluate the effect of child care problems on absenteeism of the nursing staff in the MCH Nursing Section at WBAMC.

3) Analyze and interpret collected data in order to evaluate the impact of not having a twenty-four hour child care center with facilities for employees' sick children on the absenteeism of nursing staff in the MCH Nursing Section.

Technical Approach: The primary data for this study will come from a demographic data survey, so the study design or research methodology for this study will be qualitative.

Progress: The protocol has been completed. There were 129 surveys handed out and 87 returned. A total of 52 surveys were used since they reported having children.

Abstract: A 129 self-designed questionnaires, with 41 questions, were given out to all nursing staff in the Maternal Child Health Nursing Section at William Beaumont Army Medical Center on 6 July 1993, with a personalized introduction letter. A self addressed stamped envelope for return of the questionnaire was included. The questionnaire was not coded, so there was no way of attaching data to a given individual. A total of 87 of the self-designed questionnaires were returned, which was a 68% return rate. Of these, 52 (60%) had children and 35 (40%) didn't have children. The data from the 35 MCH Nursing staff without children that returned the survey were not evaluated at this time. The 52 nursing staff in the MCH Nursing Section at WBAMC that returned the survey that have children, have a total of 106 children. Seventy one (60%) of these children are under 13 years old. The results support that the majority of nursing staff in the MCH Nursing Section at WBAMC who have children 13 years or younger, have child care problems or concerns. Of the 52 nursing staff in the MCH Nursing Section at WBAMC with children that returned the survey, fourteen (27%) have called in sick in order to stay home with a sick child and not lose salary. This supports that child care problems increase absenteeism of nursing staff in the MCH Nursing Section at WBAMC. Of the 52 nursing staff in the MCH Nursing Section at WBAMC with children that returned the survey 33 (63%) said they would utilize a twenty-four hour child care center for WBAMC employee's children, with facilities for sick children, if the cost was reasonable for this service, rather than leaving a sick child home alone, or calling in sick to stay home with a sick child to prevent loosing salary. This more than supports that nursing staff would utilize a twenty-four hour child care center for WBAMC employee's children, with facilities for sick children. This also supports that the development of a child care center for WBAMC employee's would aid in decreasing absenteeism of nursing staff.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/09 STATUS: Ongoing

TITLE: Assessment of Recalled Medical Reservists' Needs

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Dec 90 ESTIMATED COMPLETION DATE: Mar 94

PRINCIPAL INVESTIGATOR: MAJ Christine M. Piper

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Stress, Depression

Study Objective: To determine the degree of adjustment difficulty that reservists are experiencing and to assess the needs for additional support measures and programs.

Technical Approach: This study will utilize an anonymous voluntary questionnaire. This is a pilot study to survey medical and medical support reservists who were called to active duty to support Operation Desert Shield while assigned or attached to WBAMC.

Progress: No response received from investigator for FY 94 annual report.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/37 STATUS: Ongoing

TITLE: Use of Awareness of Stressors to Manage Burnout in Department of Nursing Midlevel Managers

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 92 ESTIMATED COMPLETION DATE: Mar 94

PRINCIPAL INVESTIGATOR: MAJ Christine M. Piper

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Burnout, Stress in Nursing

Study Objective: To identify current levels of burnout in midlevel nursing managers and work-related stressors and increase awareness of stressors in order to address staff burnout more effectively.

Technical Approach: This study will survey midlevel managers in Department of Nursing. Three instruments will be completed prior to an educational offering on burnout and stress management. Subjects will be asked to complete the same three instruments at 1 month, 6 months, and 2 year post workshop to identify any measured changes.

Progress: No response received from investigator for FY 94 annual report.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/10 STATUS: Terminated FY94

TITLE: How Nurses' Attitudes Affect the Way They Administer Pain Medication

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: MAJ Christine M. Piper

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): T Beeman, T Jenkins, C Moreno, L Weaver, P Payne, H Villegas

KEY WORDS: Nurses, Attitudes, Pain

Study Objective: To identify through survey: 1) current attitudes and knowledge about pain management of licensed nursing personnel at WBAMC, 2) current patient perceptions about how effectively their pain was managed during an inpatient stay, 3) nursing staff attitudes and knowledge following education about attitudes and knowledge deficits identified in the first survey, and 4) patient perceptions of effectiveness of pain management after the staff education has occurred.

Technical Approach: This study will survey all licensed nursing personnel in Department of Nursing. Nursing personnel will complete an instrument developed to measure nurses' knowledge and attitudes regarding pain. An educational program will be offered to increase knowledge and awareness in those areas identified as significant in the first survey. Following the educational offering, licensed nursing personnel will be asked to complete the same instrument. Concurrent with completion of each instrument, discharged patients will be asked to complete a questionnaire about effectiveness of management of pain while hospitalized (1 month of patients = 1200-1400, information from the last six months of 1992) to determine if there is an improvement in patient's perception of pain management following education of nursing personnel.

Progress: This protocol has been terminated, data collection completed in Sep 94.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 88/65A STATUS: Ongoing

TITLE: Pediatric Intubation Training Utilizing the Ferret Model

MONITOR (applicable for projects reviewed semi-annually): A

START DATE: Jul 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Anne Varner

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): L Tremper

KEY WORDS: Pediatric Advanced Life Support, pediatric intubation ferret

Study Objective: This training is designed to teach physicians and other health care professionals basic knowledge and endotracheal intubation skills required to resuscitate a neonate (newborn) or infant.

Technical Approach: The laboratory exercise described below will concentrate on developing the health professional's confidence in establishing an airway. Each new house officer will be required to intubate 2 ferrets employing a laryngoscope and endotracheal tube.Animals will be anesthetized with ketamine HCL (22 mg/kg, given intramuscularly), with atropine (0.04 mg/kg, subcutaneously). Up to 2 additional half-doses (11 mg/kg) of ketamine may be given if needed. Pre-anesthesia with tranquilizer (Acepromazine, 0.2 mg/kg, subcutaneously) may be given to allow easier intubation for first-time trainees. Administration and monitoring of anesthesia will be directly supervised or performed by the attending veterinarian. The veterinarian will be present at all times to assist, modify, or terminate the procedure. Butorphanol tartrate (0.2 mg/kg SC every 8 hours) will be administered after the procedure to alleviate any possible pain. At the discretion of the instructor, the stages and planes of anesthesia may be defined and assessed by the students. The animal will be placed in dorsal recumbency. Each trainee will visualize the larynx, noting the similarity of the feline larynx to that of the human infant; palpate larynx externally; and perform visual intubation using the laryngoscope and endotracheal tube. Two animals will be intubated by each first-time trainee in each laboratory session. Previously trained individuals will use one animal.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Amendment Jun 93: Feline model changed to ferret model. Principal investigator is MAJ Varner.

Progress: Ferrets are used to train nursing and medical staff on pediatric intubation.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/24 STATUS: Ongoing

TITLE: The Effect of Relaxation Therapy on Patients with Asthma

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 87 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: Helen Villegas RN

DEPARTMENT: Nursing FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Asthma Relaxation Therapy

Study Objective: To measure the effects of relaxation therapy on asthma symptoms, frequency of prn medications, and emergency medical care.

Technical Approach: Fifty intrinsic asthma patients, 20-40 years of age, followed daily in the Allergy clinic, will be involved in participating in this pilot study for 6 weeks. History and biographical data will confirm the diagnosis of intrinsic asthma. Pulmonary function tests (PFT) will be measured on the first visit. PFT will also be recorded on the second and last visit. Patients will keep an asthma diary which will document daily peak expiratory flow rate, asthma symptoms, assessment of mood and use of prn medications and medical care. After 3 weeks, subjects will return to the Allergy Clinic with their completed diaries. Their PFT will be recorded. They will be instructed in the use of a relaxation tape to use each morning upon awakening and each night after retiring. This relaxation tape will include facial muscle exercises and positive thoughts and imaging. Medical news in the Journal of the Medical Association reported in 1983 that the imagination can be used to relieve asthma symptoms while Connors has concluded that tension changes in the facial musculature reliably influences the PEFR. The patient will be given a new asthma diary to record the next 3 weeks. The hypothesis is that the relaxation therapy component of the patient's multifactorial therapy will improved asthma symptoms and decrease medication intake and the need for emergency medical care.

Progress: There has been fourteen subjects entered with no noted adverse reactions. Due to staff shortage, we have not been able to recruit 10 additional patients for the control group. The pilot study was completed using the patients as the control group before they were taught the relaxation therapy, but decided the study would be more scientific with a control group.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/02 STATUS: Terminated FY94

TITLE: Cervical Density: A Longitudinal Study to Determine Normative Values in Pregnancy

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 92 ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Philip Bayliss

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Cervical Density

Study Objective: The objectives of this study are to establish normative values for cervical density during pregnancy in uncomplicated pregnancies.

Technical Approach: A longitudinal study of nulliparous and multiparous women will be conducted. Each patient will be followed monthly from entry until delivery with cervical measurements. The patients will be recruited into this protocol from the routine obstetrical clinics at WBAMC. They will undergo serial transvaginal ultrasounds beginning at 16 weeks of gestation and continuing every 4 weeks until delivery. The images obtained of the cervix will be captured into a graphic file format for the personal computer. These files will be analyzed using densitometry software to establish a density score for the cervix. These scores will then be plotted to establish normative values for specific gestational ages.

Progress: This protocol has been terminated because computer program initailly acquired for use is not providing information as led to believe from company. Dr. Bayliss the principal investigator, has left the military service.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/03 STATUS: Terminated FY94

TITLE: Cervical Density Measured via Ultrasound: A Predictor of Risk for Preterm Delivery?

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 92 ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: MAJ Philip Bayliss

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Rosa

KEY WORDS: Cervical Density, Preterm Delivery

Study Objective: The objective of this study is to measure cervical density and to determine if it correlates to either preterm labor or delivery.

Technical Approach: A prospective, pilot study of the measurement of cervical density by computer assisted ultrasonography will be conducted. Pregnant patients from the Dept. of OB/GYN will be recruited for enrollment in this study. Two groups will be established. The first will consist of patients with no identifiable risk factors for preterm delivery and the second group with one or more of these risk factors identified. Each patient will undergo an endovaginal ultrasound for cervical length and dilatation between 22-26 weeks of gestational age. Images of the cervix for each patient will be captured into a computer by a digitizing process. These images then will be analyzed for an estimation of density of the cervix. Pregnancy outcomes will be matched with the ultrasound data to determine if cervical density scores are predictive for preterm labor or birth.

Progress: This protocol has been terminated due to computer program initially acquired for use it not providing information as led to believe from company. Principal investigator, MAJ Phillip Bayliss has left the military service.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/23 STATUS: Ongoing

TITLE: Effect of Psyllium Fiber Wafers on Serum Glucose Levels after One Hour 50 Gm Glucose Screening Test in Pregnant Patients

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 94 ESTIMATED COMPLETION DATE: Jan 95

PRINCIPAL INVESTIGATOR: CPT J. Scott Bembry

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): Dr. Butterfield

KEY WORDS: Fiber Wafers, Serum Glucose Levels

Study Objective: To determine if dietary fiber supplementation (using commercially available flavored psyllium wafers) influences glucose tolerance in pregnant patients.

Technical Approach: Two groups of obstetric patients will be enrolled. One group will consist of 10 patients of ideal body weight (IBW) and the other will consist of 10 obese patients (>150% IBW). All patients will undergo the standard diabetes screening at 24 - 28 weeks EGA, consisting of a 50 gm glucola challenge with serum glucose determination 1 hour later. These patients will then supplement their preexisting diets by consuming Metamucil wafers (2 wafers QID) for 72 hours. The patients will then repeat the 50 gm glucose challenge test. Each patient will serve as her own control.

Progress: There were 2 subjects entered in this study with no noted adverse reactions.
We are considering changing protocol to just having patients consume fiber wafers at the time of their second 1 hour DMS. This would test hypothesis and improve patient desire to participate.
The esimated completion date has changed from May 94 to Jan 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/24 STATUS: Terminated FY94

TITLE: Vaginal Hysterectomy; Morbidity with and without Injection of Epinephrine in the Vaginal Cuff

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 91 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: MAJ Philip C. Brittain

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, C Hawley-Bowland, HC Crawford

KEY WORDS: Hysterectomy, Cuff Injection

Study Objective: To determine if vasoconstrictor use in vaginal hysterectomy increases the incidence of cuff infections and to determine if vasoconstrictor use significantly reduces blood loss during vaginal hysterectomy.

Technical Approach: Patients scheduled for elective vaginal hysterectomy will be prepared for surgery in the usual fashion. The cervicovaginal junction will be injected circumferentially in each patient with 10cc's of one of the solutions described below. All patients will be given similar antibiotic prophylaxis. Estimates of blood loss will be made in conjunction with operating room staff and anesthesia. Postoperative hematocrits will be drawn at similar intervals. Intravenous fluid replacements will be at a 3:1 ratio to estimated blood loss. Specific analysis of what constitutes a postoperative wound infection will be standardized; localized abscess, erythema, marked tenderness, temperature elevation, rising white blood cell count/increasing percentage of immature forms on peripheral smear, tissue necrosis, frank pus, temperature >38 c, negative chest x-ray, and negative cultures of blood and urine. Cuff closures will be standardized among surgeons in the study.

In a double blinded randomized fashion, the pharmacy at William Beaumont Army Medical Center will prepare and code the solution to be injected. The study group will be injected with a dilute solution of epinephrine (1:200,000) in sterile saline, and a control group with sterile saline. Only at the conclusion of the study will the code be broken and data analyzed.

Progress: Principal investigator PCS. No one followed up so protocol has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/34 STATUS: Completed FY94

TITLE: GOG #95/SWO6 #9047, Randomized Clinical Trial for the Treatment of Women with Selected Stage IC & II (A, B, C) and Selected Stage IA & IB Ovarian Cancer

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Oct 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Ovarian Cancer

Study Objective: To determine if a short course of chemotherapy is more effective than intra-peritoneal radioisotope therapy in the treatment of early stage ovarian cancer and to determine the relative toxicity of each treatment.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): Study has been terminated by GOG.
Annual Review: Study was terminated on semi-annual review in April 1994. It is to early to make comments on the statistical analysis at this point. Because there has been one patient enrolled on this protocol at WBAMC, the protocol will remain open during the follow up period of this patient. Principal investigator has changed from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/67 STATUS: Ongoing

TITLE: GOG #90, Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction followed by Vincristine, Dactinomycin and Cyclophoshamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Nov 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Ovarian Germ Cell Cancer

Study Objective: To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP) followed by consolidation with vincristine plus dactinomycin plus cyclophoshamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors. To evaluate the effect of BEP chemotherapy in patients with recurrent or progressive disease during or after previous non-cisplatin containing chemotherapy. To further investigate the relevant prognostic factors. To evaluate the acute and chronic toxicity of such chemotherapy. particularly in gonadal and reproductive function. To evaluate the effect of chemotherapy on menstrual status and reproductive function in patients in whom the uterus and one tube and ovary are preserved.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date. Protocol is still ongoing.
Annual Review: No patients enrolled to date. There was a change of principal investigaror from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/68 STATUS: Ongoing

TITLE: GOG #93, Evaluation of intraperitoneal chromic phosphate suspension therapy following negative second-look laparotomy for Epithelial Ovarian Carcinoma

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Oct 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Ovarian Epithelial Cancer

Study Objective: To evaluate the efficacy of P32 therapy in patients with no residual ovarian cancer and to evaluate the morbidity from intraperitoneal P32 therapy.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (April 94): No patients have been enrolled to date. Protocol is still ongoing. Annual Review: No patients enrolled to date. There has been a change of principal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/30 STATUS: Ongoing

TITLE: GOG #122, Whole Abdominal Radiotherapy versus Circadian-Timed Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Endometrial Carcinoma (Advanced)

Study Objective: To compare treatment outcomes (survival and progression free interval) and failure patterns in patients with stages III and IV endometrial carcinoma (< 2cm residual disease) treated with whole abdominal irradiation versus circadian-timed combination doxorubicin-cisplatin chemotherapy. To determine and compare the incidence and type of acute and late adverse events observed with the two treatment regimens.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): One patient has been enrolled.
Annual Review: No patients have been enrolled to date. There has been a change in principal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/34 STATUS: Ongoing

TITLE: GOG #109, A Randomized Comparison of 5-Fu Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy versus Radiation Therapy Alone in Selected Patients with Stages IA2, IB and IIA Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Cervical Carcinoma

Study Objective: To determine whether the combination of 5-fluorouracil (%-FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive pelvic lymph nodes, positive parametrial involvement or positive surgical margins following radical hysterectomy and lymph node dissection for stages IA2, IB, and IIA carcinoma of the cervix. To determine the increase in toxicities due to 5-FU and cisplatin as an adjunct to radiation therapy versus radiation therapy alone.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date.
Annual Review: No patients enrolled to date. There has been a change of principal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/35 STATUS: Completed FY 94

TITLE: GOG #132, A Phase III Randomized Study of Cisplatin (NSC #119875) versus Taxol (NSC #125973) versus Taxol and Cisplatin in Patients with Suboptimal Stage III and IV Epithelial Ovarian Carcinoma

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Apr 95

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYB FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Epithelial Ovarian Carcinoma

Study Objective: To determine the relative efficacy of regimens consisting of taxol, versus cisplatin and versus a combination of the two drugs in patients with suboptimally debulked epithelial ovarian cancer; to determine which of the three regimens contribute most favorably to progression free interval and survival; and to compare the incidence of audiologic sequela and other toxicities from either of the three regimens.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): One patient has been enrolled with no adverse complications or reactions.
Annual Review: The GOG protocol has been closed for enrollment on a national basis. However, an individual was enrolled at WBAMC. The protocol is completed as far as additional patient enrollment, but will need to be continued until this patient completes follow up. Principal investigator has changed from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/51 STATUS: Ongoing

TITLE: GOG #114, Phase III Randomized Study of IV Cisplatin and Cyclophosphamide vs IV Cisplatin and Taxol vs High Dose IV Carboplatin followed by IV Taxol and Intraperitoneal Cisplatin in Patients with Optimal Stage III Epithelial Ovarian Carcinoma

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Sep 92 ESTIMATED COMPLETION DATE: Aug 97

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Epithelial Ovarian Carcinoma

Study Objective: To compare recurrence-free interval, complete pathologic response, and survival between the standard regimen of intravenous cisplatin/cyclophosphamide and the two experimental regimens: (1) Intravenous cisplatin/taxol and (2) intraperitoneal carboplatin followed by intravenous taxol and intraperitoneal cisplatin in patients with optimal (<1 cm residual) Stage III epithelial ovarian carcinoma. To compare the toxicities and complications of the three treatment regimens. To correlate serial serum CA-125 levels with negative second look and recurrence-free interval.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): One patient has been enrolled to date with no adverse side effects. Annual Review: Two patients have been enrolled at WBAMC with no complications or adverse events. There has been a change of principal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/52 STATUS: Ongoing

TITLE: GOG #135, Evaluation of Drug Sensitivity and Resistance with the ATP-Cell Viability Assay (ATP-CVA)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 92 ESTIMATED COMPLETION DATE: Aug 97

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: ATP-CVA, ATP, Cell Viability

Study Objective: a.To evaluate the correlation between the ATP-cell assay and patient response to chemotherapy in untreated primary epithelial ovarian carcinoma; to correlate laboratory esults with the achievement of pathologic CR at time of second look surgery; to correlate laboratory results with progression-free survival; and to correlate single agent and combined agents in vitro studies with clinical outcome. Single drugs as well as drug combinations will be tested in vitro.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date. There has been a change in principal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/63 STATUS: Ongoing

TITLE: GOG #134/NCCTG #92-61-51, A Phase III Trial of Taxol at Three Dose Levels and C-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Sep 92 ESTIMATED COMPLETION DATE: Sep 97

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Ovarian Carcinoma

Study Objective: To determine if the dose of Taxol affects response rate, progression free interval or survival in patients with platinum-resistant ovarian cancer; to compare the toxicities of the three regimens; to compare the efficacy and toxicity of two dose levels of G-CSF (5 micrograms/kg/day versus 10 micrograms/kg/day) in patients who receive the highest Taxol dose (250 mg/m2); and to determine the relationship between peak Taxol plasma concentration and toxicity/response.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date.
Annual Review: No patients have been erolled to date. There has been a change of principal investor from LTC Andrew P. Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/14 STATUS: Ongoing

TITLE: GOG #136, Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying Causes, Diagnosis, Prevention and Treatment of Ovarian Cancer

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 93 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Ovarian Carcinoma, Tumor Bank

Study Objective: To accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions; to provide a repository for long term storage of ovarian tumor, tissue, and serum. This material will be used in studies to better understand the molecular biology of ovarian tumors; and to make available. through the Cooperative Human Tissue Network (CHTN), tumor tissue and serum for proposed projects conducted by GOG Investigators (internal bank) and by researchers nationally (external bank).

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Three patients have been enrolled with no adverse reactions. There has been a principal investigator. change from LTC Andrew P. Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/21 STATUS: Ongoing

TITLE: GOG #140, An Assessment of Age and Other Factors Influencing Protocol versus Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 93 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Epithelial Ovarian Cancer

Study Objective: To assess the frequency at which patients with epithelial ovarian cancer are enrolled in prospective clinical studies at institutions participating in gynecologic oncology group protocols; to assess whether patient age affects enrollment in prospective gynecologic oncology group protocols; and to assess what demographic or clinicopathologic factors affect patient enrollment in prospective gynecologic oncology group protocols.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date. There has been a principal investigator change from LTC Andrew P. Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/42 STATUS: Ongoing

TITLE: GOG # 9207, Laparoscopic retroperitoneal lymph node sampling followed by immediate laparotomy in women with cancers of the cervix

MONITOR (applicable for projects reviewed semi-annually): LTC Thomas Gormley

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Oct 98

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Laparoscopic, Cancer of Cervix

Study Objective: To determine the adequacy of laparoscopic sampling of pelvic and aortic lymph nodes by immediate laparotomy in women with cancers of the cervix.

To obtain information of adverse effects and difficulties associated with laparoscopic sampling of pelvic and aortic lymph nodes.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (April 94): No patients have been enrolled to date. Protocol is still ongoing. Annual Review: No patients have been enrolled to date. There was a change of pricipal investigator from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/48 STATUS: Ongoing

TITLE: GOG # 144, Molecular genetic analysis of ovarian cancer families

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Jay W. Carlson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Genetic Analysis, Ovarian Cancer Families

Study Objective: 1.) To determine the frequency of chromosomal rearrangements in women with familial ovarian cancer.

2.) To identify genetic markers linked to familial ovarian cancer.

3.) To identify deletions or rearrangements that signal the site of the mutation.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: No patients enrolled to date. There has been a principal investigator change from LTC Andrew Soisson to MAJ Jay W. Carlson.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/63A STATUS: Ongoing

TITLE: Certification Training: Advanced Laser Laparoscopic GYN Procedures in the Porcine Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Carla Hawley-Bowland

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Surgical Training: Advenced Laser Laparoscopic Gyn Procedures.

Study Objective: To provide training and certification of OB-GYN Surgery Staff in laser and non-laser laparoscopic and vaginal surgical procedures. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

Technical Approach: The ability to suture during laparoscopy greatly expands the indications for laparoscopic surgery and increases the confidence of the surgeon performing more difficult procedures. There will be two live animal surgical stations and one station where some procedures will be taught with inanimate tissue such as bovine tongue and uterus. After the skin is prepped, an insufflation needle will be inserted near the umbilicus and the abdomen will be filled and maintained with 15mm Hg pressure of CO2. The insufflation needle will then be removed and replaced with a trocar/cannula for introduction of the video laparoscope which will enable monitoring of the procedure on a video screen. Two to three additional trocars/cannulas will be placed for introduction of laparoscopic graspers, scissors, laser fibers, etc. Training will involve extracorporeal and intracorporeal suturing techniques of various urogenital tissue through the laparoscopic cannulas. The argon-beam and ND:YAG laser will be used to train in techniques of tissue coagulation and excision. Abdominal lymph nodes will also be excised laparoscopically. Training will be conducted on endometrial ablation and tumor excision procedures with lasers and electrosurgery (roller-ball and large loop wire electrodes) via a hysteroscope. If difficulty is encountered with introduction of the scope through the vagina, the uterus will be exposed by laparotomy via a mid anterior suprapubic abdominal incision. Additional training for endometrial ablation and tumor removal will also be conducted with bovine uterus and bovine tongue, respectively.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: No subjects have been entered. This protocol was established when Sierra Medical Center provided an advanced laser laparoscopic GYN procedrues course. Training was extended to physicians at WBAMC. This protocol should remain open, should such a course be offered again in the future.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/47 STATUS: Ongoing

TITLE: The Clinical Management of Patients with Mild Dysplasia of the Uterine Cervix

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 91 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: CPT George L. Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, C Hawley-Bowland, HC Crawford

KEY WORDS: Dysplasia (mild)

Study Objective: To determine the incidence of HPV infection in young women with histologically proven mild dysplasia (CIN I) of the uterine cervix.

Technical Approach: Patients with dysplastic cervical cells detected by cytology will undergo standard colposcopic examination, colposcopically-directed biopsies of suspicious cervical lesions found during colposcopy, and endocervical curettage. Patients with the following clinical and pathologic characteristics will be considered for study entry: (a) histologically proven mild dysplasia (CIN I) of the ectocervix; (b) adequate colposcopic examination; (c) absence of dysplastic epithelium in the endocervical canal as proven by endocervical currettage. These patients will be thoroughly counseled about study entry. Samples from patients who elect to participate will undergo in-situ DNA hybridization to detect specific subtypes of HPV within cervical cells using the Vira-Type kit. Patients with even last digit SSN will receive standard therapy using cryotherapy or laser vaporization of the transformation zone of the cervix (Group A). Patients with odd last digit SSN will be assigned to the observation group (Group B). All study participants will be monitored every 3 months in the Gynecology Clinic using cervical cytology (PAP Smear), colposcopic examination, and colposcopically directed biopsies of suspicious lesions. All women will be followed for a minimum of 2 years. The sexual consorts of study group patients will be referred to the Male Dysplasia Clinic in the OB-GYN Clinic for Vira Type, colposcopy and colposcopically directed biopsies.

Progress: Thirty-eight subjects have been entered to date with no adverse reactions.There has been a pricncipal investigator change from MAJ Philip C. Brittain to CPT George L. Maxwell. Completion date has been extended to June 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/30 STATUS: Completed FY94

TITLE: Angiogenesis as a Histopathological Prognostic Feature for Uterine Cervical Dysplasia and Invasive Carcinoma

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: CPT George L. Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Brittain, A Soisson, T Casey

KEY WORDS: Angiogenesis, Histopathological

Study Objective: To determine if microvessel counts in cervical cone biopsy specimens of patients with cervical dysplasia correlates with the histologic grade of dysplasia and
to determine if microvessel counts in hysterectomy and biopsy specimens in patients with invasive cervical cancer correlate with other known prognostic factors and with survival.

Technical Approach: (1) All patients with cervical dysplasia who have undergone a cone biopsy at William Beaumont Army Medical Center in the past 3 years will be identified by review of operative logs; (2) All patients with invasive cervical cancer who have undergone cervical biopsy or hysterectomy in the past 3 years at William Beaumont Army Medical Center will be identified by review of the operative and pathology logs; (3) Histologic sections from the patients cone biopsy, cervical biopsy, or hysterectomy containing the dysplastic lesion or carcinoma will be prepared using standard techniques from paraffin embedded tissues; (4) Two slides from each patient will be prepared. One slide will be stained with hematoxylin-eosin to grade the tumor and the dysplastic lesion. One slide will be stained with anti-factor eight antibody to count the number of vessels in the following fashion: (a) Each slide will be de-paraffinized and rehydrated utilizing standard techniques; (b) Tissues will be stained with anti-factor 8 antibody to highlight microvessels using a standard immunoperoxidase technique; (c) The area of highest neovascularization will be determined by Doctor Casey and subjectively graded on a scale from 1-4+, individual microvessels will be counted on a 200X field (20X objective lens and 10X occular lens; (d) Microvessel counts will be compared with degree of dysplasia for patients with preinvasive disease and with other prognostic factors and survival in patients with invasive carcinoma.

Progress: Study has been completed. Approximately ninety subjects were entered. Paper was completed and has been submitted to the American Journal of Obstetrics and Gynecology. There was a change of principal investigator from CPT Joel Webb to CPT George L. Maxwell.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/31 STATUS: Ongoing

TITLE: Loop Electrosurgical Excision Procedure Treatment for Dysplasia of the Uterine Cervix

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 93 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: CPT George L. Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, P Miles

KEY WORDS: Loop, Dysplasia, Cervix

Study Objective: (1) To compare methods of preparation of the cervix prior to Loop Electrosurgical Excision Procedure (LEEP) in treatment of cervical dysplasia. Specifically, to determine if colposcopic visualization of the dysplastic lesion or the absence of staining by iodine containing solutions on dysplastic lesions is a more efficacious method of defining the full extent of the lesion prior to excision.

(2) To determine the success rate of treatment of cervical dysplasia with LEEP, based on cytologic analysis of surgical specimens.

Technical Approach: (1) Patients with dysplastic cervical cells detected by cytology from Pap smears will undergo standard colposcopic evaluation, colposcopically directed biopsies of suspicious cervical lesions, and endocervical curettage.

(2) Patients with the following clinical and pathologic characteristics will be considered for study entry:
a) histologically proven dysplasia of the ectocervix,
b) adequate colposcopic examination,
c) proven absence of dysplastic epithelium in the endocervical canal by endocervical curettage.

(3) Patients with these characteristics will be thoroughly counseled about study entry.

(4) The patients enrolled in the study will be treated with LEEP using standard protocols. A paracervical anesthetic block will be performed with 10cc 1% xylocaine with 1:100,000 epinephrine. Loop electrosurgical excision will be performed with bipolar cutting/coagulation wire loops using a Valley Lab Electrosurgical generator unit and large wire loops when possible (for better specimen analysis). Patients will be randomized by pseudo number generation to colposcopy followed by LEEP or application of Lugol solution to the cervix followed by LEEP of the non-staining areas. Comparison will be made to LEEP specimens collected using Lugol's solution for demarcation of the cervical abnormal epithelium, on the principle that normal squamous epithelium contains enough glycogen to stain and dysplastic tissue does not. Neither of these preparation techniques, however, are foolproof and both false positive and negative areas may be highlighted. We seek to determine whether colposcopy/LEEP is more efficacious than Lugol/LEEP, the surgical margins will be evaluated by standard histopathologic techniques. Treatment success will be analyzed 3 months after therapy when colposcopy and cervical cytology is performed.

Progress: Thirty subjects have been entered to date with no noted adverse reactions. There was a principal investigator change from MAJ Philip C. Brittain to CPT George L. Maxwell. Completion date has been extended to June 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/39A STATUS: Ongoing

TITLE: The Hemodynamic Response of Meconium Infusion in a Pregnant Sheep Model: Attempted Simulation of the Amniotic Fluid Embolism Syndrome

MONITOR (applicable for projects reviewed semi-annually): COL Stephanie Sherman

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, PC Brittain, RA Harris, P Bayliss, M Kestner, J Galloway, P Miles

KEY WORDS: Simulation Sheep, Amniotic Fluid, Embolism Syndrome

Study Objective: The purpose of this blinded prospective randomized controlled trial will be to study the effects of intravenous injection of meconium and amniotic fluid on hemodynamic function and subsequent cardiopulmonary pathology in the sheep model.

Technical Approach: A total of 16 pregnant sheep over 130 days gestation (corresponding to a near term human pregnancy) with a confirmed singleton fetus will be used to investigate the effects of intravenous infusion of meconium emboli. The pregnant sheep will undergo placement of a Swan-Ganz jugular catheter and carotid arterial catheter to evaluate the hemodynamic changes associated with infusion of the amniotic fluid specimens. Baseline hemodynamic measurements will be obtained one hour after placement of the Swan-Ganz and carotid catheters with the animal unanesthetized restrained in a standard sheep stanchion with head gate. Two samples of amniotic fluid will be used for injection: light meconium stained and thick meconium stained amniotic fluid. The animals will be divided into two groups according to the type of meconium stained amniotic fluid that will be infused (light or thick stained fluid): two animals will receive intravenous saline (control), two will receive unstained amniotic fluid, six will receive light meconium stained amniotic fluid, and six will receive thick meconium stained amniotic fluid. In the 12 animals that will receive meconium stained amniotic fluid, 2 will be infused with whole light meconium stained fluid, 2 will receive whole thick meconium stained fluid, 2 will receive the supernant from light meconium stained fluid, 2 will receive the supernant from thick meconium stained fluid, 2 will receive the precipitate from light meconium stained fluid, and 2 will receive the precipitate from thick meconium stained fluid. The investigator administering the solutions will be blinded to the identity of the infused substances. Following infusion into the venous system, hemodynamic parameters will be measured for the first hour after infusion. Doppler echocardiography will be used to determine cardiac ejection fractions at the time of infusion and at one hour post-infusion. After euthanasia has been performed, histologic sections from each animal's lung will be submitted to the pathology department for analysis and confirmation of amniotic fluid embolism. Data obtained before and after infusion of the various substances will be compared statistically.

Amended #1, May 1994: Original protocol is being finished with inclusion of the remaining animals. An additional 16 animals will be utilized to investigate the effects of hypoxia on meconium embolism. COL Sherman has been designated as veterinary medical monitor.

Progress: There have been nine subjects enrolled with no documented adverse reactions. Completion of study is pending arrival of final seven animals. The estimated completion date has been extended from January 94 to October 94.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/51 STATUS: Ongoing

TITLE: A prospective randomized comparison of tocolysis and expectant management after mature fetal lung studies

MONITOR (applicable for projects reviewed semi-annually): MAJ Jay Carlson

START DATE: Sep 93 ESTIMATED COMPLETION DATE: June 95

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Bayliss

KEY WORDS: Tocolysis Mature Fetal Lung

Study Objective: The purpose of this study is to determine the role of tocolytic therapy in preterm labor patients once fetal lung maturity has been established.

Technical Approach: This is a prospective and randomized study. All preterm labor patients with biochemical evidence of lung maturity will be randomized into a tocolytic or expectant management group. Maternal and neonatal outcomes will be compared.

Progress: Semi-Annual Report (April 94): Patients are being recruited slowley, secondary to a limited number of "mature taps," as well as some patietns declining to enter the study. In addition, the machine that runs the FLM test has been broken periodically. We are continuin the study.
Annual Report: Nine patients have been enrolled to date. There have been no documented adverse reactions. The principal investigator changed from CPT Christopher Benson to CPT G. Larry Maxwell. The estimated completion date has been extended from May 94 to June 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/55A STATUS: Completed FY94d

TITLE: Repair of Transversely Incised Anterior Abdominal Rectus Fascia: Optimization of Technique

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, PC Brittain, RA Harris, P Miles, T Scully

KEY WORDS: Transversely Incised Rectus Fascia

Study Objective: The purpose of this prospective randomized study will be to determine the most effective method of closing transversely incised lower anterior abdominal rectus fascia.

Technical Approach: A total of thirty six rabbits will be used in the study. Each animal will be randomly assigned to one of three postoperative interval groups: one week, two weeks and four weeks. Four to five transverse abdominal incisions will be made on each animal under general anesthesia, each incision being 8cm in length, extending through the anterior rectus fascia. Six groups of fascial suture repair will be investigated using 0-Dexon: Group I, a continuous running suture with 1cm bites taken at 1cm intervals; Group II, a continuous running suture with 2cm bites taken at 1cm intervals; Group III, a continuous running suture with 1cm bites taken at 0.5cm intervals; Group IV, interrupted sutures involving 1cm bite taken at 1cm intervals; Group V interrupted sutures involving 2cm bites taken at 1cm intervals; and Group VI, interrupted sutures involving 1cm bites taken at 0.5cm intervals. Groups II and III will involve using a suture long enough to maintain a SL/WL of 4 as previously mentioned. All randomization will be performed using a pseudorandom number generating program.

Upon completion of the assigned postoperative period, each animal will undergo euthanasia as described in animal procedures. Each 8cm fascial incision will then be removed "in bloc" and subsequently trimmed into 8 separate 2cm x 1cm strips. Three strips representative of separate wounds from each of the six repair groups (total of 18) will be submitted for pathology analysis to compare the degree of necrosis associated with each repair technique. The remainder of the tissue specimens will be frozen in liquid nitrogen and stored until analysis of tensile strength.

Tensile strength will be determined using an Instron materials testing system located at Texas Tech in conjunction with William Beaumont's Department of Orthopedics. Each tissue specimen will be randomly assigned to one of two measurement groups: intrinsic wound strength determined after removal of suture and extrinsic wound strength determined with suture left in place. Tensile strength will be defined as the force needed to separate the tissue specimen at the incision.

Progress: Sixteen subjects were entered with no noted adverse reactions. Tissue awaiting analysis to finish the study.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/25 STATUS: Ongoing

TITLE: Perinatal Transmission Rates of Human Papilloma Virus in Various Maternal Fluids

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 94 ESTIMATED COMPLETION DATE: June 95

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Zacharean, JW Carlson, AP Soisson, WF Nauschuetz, F Harlass

KEY WORDS: HPV, Prenatal Transplacental Transmission

Study Objective: The purpose of this prospective blinded trial is two-fold:

1) To determine the incidence & respective viral DNA type of HPV in cervical & peripheral blood specimens of pregnant patients.

2) To determine the perinatal transmission rate of HPV by perinatal analysis of transabdominally collected amniotic fluid as well as maternal/fetal blood and breast milk taken immediately postpartum.

Technical Approach: A total of 100 patients will be entered in this prospective study. It is a collaborative study between WBAMC and Texas Tech. Each patient will have cervical swab & amniotic fluid samples analyzed for HPV type using PCR amplification techniques. Maternal and cord blood samples and breast milk samples will be analyzed on those patients identified as HPV positive; similar techniques will be used in determining the presence and type of HPV. Questionnaires will also be filled out on each participant in order to provide demographic data for statistical comparison (i.e., age, gravidy, paridy, smoking history, race, sexual history, past medical problems, history of abnormal PAP smears, indication for amniocentesis, gestational age).

Amendment #1 (Apr 94): Changed title from "Determination of Prenatal Transplacental Transmission Rates of HPV in an Infected Pregnant Population" to present title. Added breast milk as sample to be obtained. Added M Zacharean as an associate investigator.

Amendment #2 (May 94): Funding implications modified.

Progress: Fourty-five patients have been entered to date with no adverse reactions.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/30 STATUS: Ongoing

TITLE: Detection of Human Papillomavirus in Ovarian and Uterine Cancers Using Q-PCR

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 94 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, J Carlson, WF Nauschuetz, P Miles, KM Brady

KEY WORDS: HPV, PCR

Study Objective: The purpose of this study will be to demonstrate the presence of HPV in gynecological neoplasms other than cervical cancer (i.e., ovarian and endometrial carcinomas; uterine sarcomas) using quantitative PCR techniques.

Technical Approach: A total of 50 ovarian (Stage III and IV) and 50 endometrial (all stages) carcinomas in addition to approximately 10 uterine sarcoma cancer specimens will be identified in a collaborative effort by investigators from WBAMC and SMC. Ten benign tissue specimens (5 ovarian and 5 uterine) will be collected from each institution, providing a total of 20 ovarian controls and 20 uterine controls. Ribbons of tissue will be prepared by the pathology associate investigators Brady and Miles in conjunction with histopathology technicians at both SMC and WBAMC. The paraffin embedded tissues will be transported in glass containers to the Department of Clinical Investigations at WBAMC and stored at -70 degrees Celsius until analysis. DNA will later be extracted and analyzed for the presence of HPV using Q-PCR. The analysis will specifically determine the presence of HPV viral types 6, 11, 16, 18, 31 and 33 in each of the specimens.

Progress: Approximately 100 subjects have been entered. There have been no adverse reactions. Tissue collection is completed and charts have been reviewed. Study completion is pending analysis of samples.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/31 STATUS: Ongoing

TITLE: Messenger Ribonucleic Acid (RNA) Expression of E6/E7 Oncogenes in Cervical Carcinoma

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 94 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, J Carlson, WF Nauschuetz, P Miles, KM Brady

KEY WORDS: RNA, E6/E7

Study Objective: The purpose of this retrospective study is to demonstrate the presence of increased E6/E7 expression in cervical tumors from past cervical cancer patients.

Technical Approach: A total of 50 cervical cancer specimens will be identified in a collaborative effort by investigators from both WBAMC and SMC. Ribbons of tissue will be prepared by the pathology associate investigators Brady and Miles in conjunction with histopathology technicians at both WBAMC and SMC. The paraffin embedded tissues will be transported in glass containers to the Department of Clinical Investigations at WBAMC and stored until analysis. Messenger RNA will later be extracted and complimentary DNA produced from corresponding E6/E7 sequences in the tissue sample. This complimentary DNA will then be quantitatively detected following PCR amplification. Positive and negative controls will be provided by cell lines SiHa and K562, respectively.

Progress: Ninety subjects have been entered to date. There have been no adverse reactions. Tissue collection is completed and charts have been reviewed. Study completion is pending analysis of samples. Estimated completion date has changed from May 95 to Jun 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/34A STATUS: Ongoing

TITLE: The Use of Oxidized Regenerated Cellulose (Interseed) in Preventing Adhesions Associated with the Use of Marlex and GORE-TEX Meshes (Oryctolagus cuniculus model)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 94 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: CPT G. Larry Maxwell

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AP Soisson, RA Harris, M Wood, J Carlson

KEY WORDS: Interseed, Marlex, GORE-TEX

Study Objective: The purpose of this prospective randomized study will be to determine whether the use of Interseed reduces intra-abdominal adhesions which normally accompany the use of Marlex and GORE-TEX when used as an abdominal wall prosthesis.

Technical Approach: A total of 50 rabbits will be used in the study. Each animal will be randomly assigned to one of two postoperative interval groups: 4 days or 4 weeks. Animals will then undergo surgery to create a full-thickness abdominal wall defect approximately 3 cm square. The defect will then be randomly repaired using one of five methods: 1) closure involving rotation of a 3x3 cm vascularized pedicle of external oblique muscle and fascia; 2) closure with a 3x3 cm piece of Marlex only; 3) closure with a 3x3 cm piece of Interseed bound to the back of a similar sized piece of Marlex; 4) closure with a 3x3 cm piece of GORE-TEX only; 5) closure with a 3x3 cm piece of Interseed bound to the back of a similar sized piece of GORE-TEX. All randomization will be performed using a pseudorandom number generating program. Upon completion of the assigned postoperative period, each animal will undergo euthanasia as described in animal procedures. The abdominal wall will then be dissected from each animal and the adhesive involvement quantified. When adhesions are present, calculation of area differential (equals pretreatment area minus posttreatment area) and percent improvement (equals area differential minus [area differential/pretreatment area] x100) will be performed to determine whether the use of Interseed reduces the extent of adhesion formation. Finally, a previously described subjective scale will be used to rate the overall tenacity of resultant adhesions (none=0; adhesions fell apart=1; adhesions lysed with traction=2; adhesions required sharp dissection for lysis=3).

Progress: No subjects have been entered. Study pending arrival of animals.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/45 STATUS: Completed FY94

TITLE: Vaginal 5-Fluorouracil Therapy in the Management of Human Papilloma Virus Infections of the Cervix Uteri

MONITOR (applicable for projects reviewed semi-annually): MAJ Connie Butterfield

START DATE: May 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: CPT Peter Napolitano

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Soisson, C Hawley-Bowland, P Miles, P Day, D Smith

KEY WORDS: Cervix Uteri, Hpv, 5-Fluorouracil

Study Objective: To determine if 5-FU therapy is efficacious in eliminating HPV from the genital tract and to determine if 5-FU therapy will prevent the progression of HPV infections and minor associated cytologic abnormalities (koliocytotic atypia) to dysplasia.

Technical Approach: Patients will undergo HPV Profile, colposcopic examination, directed biopsies of suspicious lesions, and endocervical curettage (ECC). Patients with a positive HPV Profile will undergo Vira Type to further identify the subtype of the virus. Patients with a normal colposcopic examination or when directed biopsy and ECC excludes a dysplastic process will be counseled appropriately for study entry. Patients who elect to participate will be randomly assigned to one of two treatment regimens: Group A will be assigned to the observation only arm and will be followed closely with repeat cytology, HPV Profile, and colposcopic examinations every 3 months for six months. Group B will receive 5% topical 5-Fluorouracil cream (1/4 applicator) in the vagina every night for 7 nights. Following therapy, patients will be followed in the same manner as those in Group A.

Adverse Event presented to IRB Feb 93. Patient admitted for urinary retention secondary to labial erythema and edema for accidental contact with topical 5-FU cream. No adverse sequelae.

Progress: Semi-Annual Review (April 94): Data collection is complete. Study is now in evaluation stageApproximately sixty subjects were entered with no documented adverse reactions.
Annual Review: Study completed and has been submitted for publication.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/29 STATUS: Ongoing

TITLE: Platelet Count Changes in Term, Low Risk Deliveries

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 94 ESTIMATED COMPLETION DATE: Feb 95

PRINCIPAL INVESTIGATOR: CPT Roger J. Rembecki

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Bayliss

KEY WORDS:

Study Objective: Determine platelet count changes in term, low risk deliveries.

Technical Approach: We will review the platelet counts measured at parturition and post partum (less than or equal to 48 hours). Data will be analyzed to discover significant changes chronologically and significant differences between vaginal and caeserean deliveries.

Progress: Study has just began, so no progress was reported.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/04 STATUS: Terminated FY 94

TITLE: Protocol GOG # 99, A Phase III Randomized Study of Surgery VS. Surgery Plus Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

MONITOR (applicable for projects reviewed semi-annually): LTC Elmer Pacheco

START DATE: Nov 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Endometrial Adenocarcinoma

Study Objective: To determine if patients with intermediate risk endometrial adenocarcinoma, who have no spread of disease to their lymph nodes, benefit from postoperative pelvic radiotherapy. To evaluate how the addition of radiotherapy will alter the site and rate of cancer recurrence in those intermediate risk individuals.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients have been enrolled to date.
Annual Review: At the present time there have not been patients enrolleld on this GOG Protocol at WBAMC.Although this protocol remains open on a national level, I will elect to terminate this protocol due to its difficulty to achieve patient enrolllment. The difficulty arises in the concept in randomizing a patient with intermediate risk endometrial cancer to no therapy versus standard pelvic radiation. Becuase of the extremes of the two arms it is difficult for patients to understand.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/32 STATUS: Terminated FY 94

TITLE: GOG #125, Extended Field Radiation Therapy with Concomitant 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes (Phase II)

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Cervical Carcinoma (Metastatic)

Study Objective: In this study, patients with cervical cancer who have biopsy confirmed para-aortic lymph node metastases will receive combination chemotherapy consisting of cisplatin and 5-FU intravenous infusion concomitantly with pelvic and para-aortic extended field radiation therapy. The objectives of this study are to assess progression-free survival and overall survival; sites of initial failure; and morbidity of the treatment.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date.
Annual Review: The GOG protocol #125 has been terminated for enrollment on a national basis. There were no patients enrolled on this protocol at WBAMC. Therefore, there is no reason for continuing this protocol in an ongoing or active state. No abstract will be generated from this institution.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/33 STATUS: Terminated FY94

TITLE: GOG #107, A Randomized Study of Doxorubicin (NSC #123127) versus Doxorubicin plus Cisplatin (NSC #119875) in Patients with Primary Stage III and IV Recurrent Adenocarcinoma

MONITOR (applicable for projects reviewed semi-annually): MAJ Jennifer Cadiz

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Apr 97

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland

KEY WORDS: Adenocarcinoma

Study Objective: The major objective of this study is to determine whether the addition of cisplatin to doxorubicin offers significant improvement in the frequency of objective response, the duration of progressive free interval, and the length of survival as compared to doxorubicin alone.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date.
Annual Review: The GOG protocol #107 has been terminated for enrollment on a national basis. There were no patients enrolled in this protocol at WBAMC. No abstract will be generated form this institution.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/62 STATUS: Terminated (FY 94)

TITLE: GOG #138, A Phase II Trial of Cisplatin and Cyclophosphamide in the Treatment of Extraovarian Peritoneal Serous Papillary Carcinoma

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Sep 92 ESTIMATED COMPLETION DATE: Oct 95

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Papillary Carcinoma

Study Objective: To determine the response rate, and response duration in patients with extraovarian peritoneal serous papillary carcinoma treated with a combination of cisplatin and cyclophosphamide.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: Semi-Annual Review (Apr 94): No patients enrolled to date.
Annual Review: The GOG protocol #138 has been terminated for enrollment on a national basis. There were no patients enrolled on this protocol at WBAMC. Therefore there is no reason for continuing this protocol in an ongoing or active state. No abstract will be generated from this institution.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/47 STATUS: Terminated FY 94

TITLE: GOG # 143, Familial and reproductive factors in ovarian cancer

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: LTC Andrew Soisson

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Familial Reproductive Ovarian Cancer

Study Objective: 1.) Compute prevalence rates for cancer of the ovary, breast, colon, and uterus in first and second degree relatives of ovarian cancer cases.

2.) To identify that subset of multicase families who would be candidates for linkage analysis studies in the companion GOG protocol 144.

3.) To estimate, by fitting major gene models to familial ovarian cancer incidence.

4.) To determine if established reproductive risk factors (parity, oral contraception (OC) use, tubal ligation) alter risk in women with a positive family history.

5.) To collect and store a blood sample from each participant in the study for storage and subsequent gene analysis frequency.

Technical Approach: Details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: The GOG protocol #143 has been terminated for enrollment on the national basis. There were no patients enrolled on this protocol at WBAMC. No abstract will be generated from this institution.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/08A STATUS: Ongoing

TITLE: OB/GYN Bowel Training Utilizing the Pig Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 86 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Julius Szigeti

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Surgical Training in Residency - GI

Study Objective: This training is designed to teach physicians the basic knowledge and operative skills required to perform basic small and large bowel surgery.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing bowel injuries, resecting and anastomosing small bowel, and large bowel exteriorization. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery consists of small bowel resection and re-anastomosis. The surgical site is then closed and the animal awakens from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of resecting the colon and creating a colostomy. Afterward, the surgical site will be closed and euthanasia administered while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: From 01 July 1993 to 30 June 1994, thirteen operative episodes were performed. Seven pigs were utilized with 13 operative episodes. There was one operative complication. In one pig, the small bowel anastomosis had adhered to the anterior abdominal wall. Seven residents were trained in bowel surgical techniques. There was a principal investigator change from LTC Carla G. Hawley-Bowland to MAJ Julius Szigeti as of 01 September 1994.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/33A STATUS: Ongoing

TITLE: OB/GYN Microsurgical Tubal Re-Anastomosis Training Utilizing A Rabbit Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 86 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Julius Szigeti

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Wood

KEY WORDS: Tubal Re-anastomosis, Surgical Training in Residency - Rabbit

Study Objective: This training is designed to teach resident physicians the basic knowledge and operative skills required to perform microscopic tubal surgery.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeon's confidence in utilizing the operating microscope and microsurgical instruments as well as planning and accomplishing the operative procedures. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery consists of unilateral uterine cornua resection and re-anastomosis. The surgical site is then closed and the animal awakens from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted. The first microsurgical anastomosis site will be re-explored for patency and the training procedure will be repeated on the contralateral cornua. After completion of the procedure euthanasia will be administered as described below.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: From 01 July 1993 to 30 June 1994, six operative episodes were performed. Six rabbits were utilized in six operative episodes. Six residents were trained in microsurgical tubal reanastomoses. There was a principal investigator change from LTC Carla G. Hawley-Bowland to MAJ Julius Szigeti as of 01 September 1994.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 86/64A STATUS: Ongoing

TITLE: Genitourinary Tract Surgery Training Utilizing a Pig Model and Comparing Stenting Technique

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 86 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Julius Szigeti

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Genitourinary Surgical Training Residency

Study Objective: This training is designed to teach resident physicians the basic knowledge and operative skills required to perform genitourinary surgery while simultaneously evaluating the need for ureteral stenting following the operative procedures.

Technical Approach: The laboratory exercise described will concentrate on developing the surgeons confidence in recognizing GU injuries, resecting and anastomosing ureters, and reimplanting ureters into the urinary bladder. To accomplish these training objectives, one survival and one non-survival surgical training procedure will be conducted on each animal assigned to the protocol. The first surgery will consists of unilateral ureter resection and re-anastomosis. Upon completion of this procedure, the laparotomy incision will be closed and the animal awakens from anesthesia. The surgical procedure and post operative care will be conducted as stated below. After approximately three weeks, a second laparotomy will be conducted and the training will consist of transecting the contralateral ureter at the point of entry into the urinary bladder and reimplanting the ureter through the bladder wall. Afterward, the laparotomy incision will be closed and euthanasia administer while the animal is still anesthetized.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: From 01 July 1993 to 30 June 1994, eight operative episodes were performed. Five pigs were utilized with the eight operative episodes. Six residents were trained in bowel surgical techniques. There was a principal investigator change from LTC Carla G. Hawley-Bowland to MAJ Julius Szigeti as of 01 September 1994.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/54 STATUS: Completed FY 94

TITLE: Vaginal Operative Delivery in Modern Obstetrics

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: CPT Joel Webb

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Bayliss

KEY WORDS: Vaginal Delivery, Forceps

Study Objective: To review data in the current literature to determine whether forceps delivery is a safe and viable alternative to cesarean deliveries in certain labor situations.

Technical Approach: Retrospective review of data in obstetrical literature.

Progress: Study completed as of November 1994. A Retrospective review of the literature was performed on articles since 1990 dealing with the safety of operative (forceps) vaginal deliveries. The data supported the recent ACOG committee opinion that forceps deliveries from the low and outlet categories are safe with minimal neonatal morbidity and maternal morbidity comparable to spontaneous vaginal delivery. The data also showed that forceps deliveries matched by station with cesarean deliveries are associated with increased neonatal injury from the higher stations. Cesarean deliveries from the lower stations were associated with unjustifiable maternal morbidity compared with forceps deliveries from the same station. Overall, the safety of low and outlet forceps deliveries for the accepted indications was supported. The estimated completion date has changed from Dec 93 to Nov 93.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/28 STATUS: Ongoing

TITLE: Evaluation of Phenobarbital in the Prevention of Intraventricular Hemorrhage in the Very Low Birth Weight Infant (<1500gms or 32 Weeks)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: CPT Gary C. Wharton

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): FE Harlass

KEY WORDS: Intraventricular Hemorrhage, Phenobarbital

Study Objective: To retrospectively compare WBAMC records where the current standard of care includes phenobarbital administration to any mother suspected or imminently delivering an infant 15gms or less, to those of R. E. Thomason General Hospital (RETGH), where the current standard of care does not include this administration. Through this comparison, an attempt will be made to demonstrate that such administration is beneficial in reducing the incidence and severity of intraventricular hemorrhage in this population as previously suggested.

Technical Approach: This will be a retrospective case controlled analysis of maternal and infant records. WBAMC's experience will be controlled with the experience at RETGH.

Progress: Protocol delayed due to lack of research time for computation of data. Still interested in project hope to complete in very near future. All data collected but not analyzed. Estimated completion date has changed from Jan 95 to indefinite.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/19 STATUS: Completed FY 94

TITLE: Management of Inflammatory Cytologic Abnormalities Detected by Papanicolaou Smears: A Randomized, Prospective Study

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 93 ESTIMATED COMPLETION DATE: Feb 95

PRINCIPAL INVESTIGATOR: CPT Gary C. Wharton

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Hawley-Bowland, J Webb

KEY WORDS: Inflammatory Cytologic Abnormalities, Papanicolaou Smears

Study Objective: To prospectively evaluate the efficacy of three therapeutic regimens of metronidazole versus a control, on the course of inflammatory cytologic abnormalities.

Technical Approach: 400 female Patients will be randomized into 4 groups using a sequential randomizing system. These groups will consist of: Group A: Metronidazole 500mg po bid x 7 days; Group B: Metronidazole 2gms po x one dose; Group C: Metronidazole gel (0.75%) 5gms intravaginally bid x 5 days; Group D: Control, no treatment.

Progress: One-hundred and sixty subjects were entered in the study, two withdrew. There were no noted adverse reactions. All subjects have been entered. Data to be analyzed. Results are forthcoming. Estimated completion date has changed from Jan 94 to Feb 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/38 STATUS: Ongoing

TITLE: Sterilization Regret in a Military Population

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 94 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ Michael Wood

DEPARTMENT: OB/GYN FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Sterilization

Study Objective: Among women in a military population who seek reversal of tubal ligation, to determine what factors they identified as responsible for their desire to overturn a permanent procedure.

Technical Approach: Questionnaire

Progress: Study has just begun. There is no data to report as yet.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/47A STATUS: Completed FY94

TITLE: The Effect of Bovine TSH on Hemoglobin Proportions in Adult Rats

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 92 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: MAJ Jack T. Pearson

DEPARTMENT: Pathology FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Critz, D McKell, J Enriquez, KM Brady, T Baker

KEY WORDS: Hemoglobin

Study Objective: Test bovine TSH's effect on rat hemoglobin chromatogram patterns.

Technical Approach: Phase I: In this phase five adult animals and the litter from one timed pregnancy will be used to gain familiarity with the procedures to be used in this protocol (and described below); cardiac puncture, intraperitoneal injection, performance and preparation of chromatography.

Phase II: This phase will be used to repeat Gilman and Datta's chromatograms. However rather than classic liquid chromatography, this project will utilize HPLC. Twenty adult rats and the litters from 6 timed pregnancies will undergo cardiac puncture. The specimen will be chromatographed. The chromatograms will be compared to establish the previously observed difference in the adult and neonatal pattern and subsequently compared to Gilman and Datta's work.

Phase III: In this phase, 10 adult rats will each be dosed with different concentrations of bovine TSH. After one week, a cardiac puncture will be performed and the specimens tested for T3 RIA and T4 levels. The dose producing a level of hyperthyroidism which is three times normal will be chosen for phase IV.

Phase IV: In this phase, 20 adult animals will have an intraperitoneal injection of bovine TSH. The control group will also consist of 20 adult animals and will receive an injection of sterile normal saline. Each week a cardiac puncture will be performed and the specimen chromatographed.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Amended Sep 93, approved Sep 93: Deleted T Casey, added T Baker as associate investigator. Deleted K O'Hair, added R Harris as attending veterinarian. Changed completion date to Jun 94.

Amended Jan 94, approved Jan 94: Phase IIb, IIIb amended. Copy on file at DCI. Number of rats required increased from 75 to 142.

Progress: Principal investigator has PCS'd from the Army. Protocol has been completed.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/01 STATUS: Ongoing

TITLE: Retrospective Analysis of the Association between Attention Deficit Disorder and Central Auditory Processing Problems

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 92 ESTIMATED COMPLETION DATE:
May 95

PRINCIPAL INVESTIGATOR: COL Alva W. Atkinson

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Dennis, MC Knott, D Penow

KEY WORDS: ADD, CAPP

Study Objective: Two hyptheses will be addressed: (1) Central auditory processing problems (CAPP) occur in high frequency (>20%) among patients diagnosed with Attention Deficit Disorder (ADD) and (2) the incidence of CAPP in ADD will be represented equally among the subtypes of ADD (ADD with hyperactivity and ADD without hyperactivity).

Technical Approach: The medical records of patients assessed by Developmental Pediatrics Clinic for ADD and by Audiology and Speech/Language Clinics during 1989-1990 will be reviewed. Data will be collected for age, grade, diagnoses, auditory and language evaluation results. Specifically, data from the audiologic assessment data from the SCAN (central auditory processing battery) will be collected. From the language evaluation, the overall receptive and expressive language assessments (normal, mild moderate, or severe) and the TOKEN test results will be noted. Data will be studies for frequencies and association using descriptive and simple comparative statistics. The investigators consider this a pilot study which will potentially be the basis of a prospective, more tightly controlled large study.

Progress: There has been 100 subjects entered in the study with no noted adverse reactions. Slow progress but ongoing at this time. The estimated completion date has been changed from Jan 94 to May 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/27 STATUS: Ongoing

TITLE: Male Adolescent Attitudes about Condom Use and Barriers to Effective Use

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 94 ESTIMATED COMPLETION DATE: Aug 94

PRINCIPAL INVESTIGATOR: LTC Denise C. Cabeza

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JD Foley

KEY WORDS: Male, Adolescent, Attitudes, Condom

Study Objective: 1. To identify the obstacles encountered in obtaining condoms.
2. To understand the reasons why teens do not use condoms.
3. To identify factors which result in condom failure or improper use.

Technical Approach: All adolescent males between the ages of 15 to 21 years who seek health care at the Adolescent Clinic WBAMC, will be provided with a self-administered questionnaire (attached). Teens who are not sexually active will complete demographic data only. Teens, who acknowledge past sexual activity on the questionnaire, will continue on and complete the remainder of the questionnaire. Responses will be made by circling the best answer from five choices arranged on a "Likert" scale format for each question. The respondent will remain anonymous. Completed questionnaires will be placed by the patient in a defined, secure receptacle. Participation in the study will be completely voluntary. At the end of 6 months this data will be collected, analyzed and submitted as an article format to the Dept. of Clinical Investigation.

Progress: There were 350 subjects entered in this study with no noted adverse reactions.

Abstract: It has long been recognized that a treatment for beta hemoglobin chain anomalies could result if a way to reverse the hemoglobin F to hemoglobin A switch in humans was found. Studies of hemoglobin switching have been hampered by the fact that small animals normally used in the laboratory do not have a true Hemoglobin F. However, several small animal models which take advantage of a switch in minor beta chain proportions in certain strains of inbred mice and rats have been proposed and used. The use of these models have suffered from what, until now, could be considered technically demanding, time consuming methodologies. In this study we report an effective, rapid and technically streamlined model of hemoglobin switching utilizing Fisher 344 rats and high precision liquid chromatography with a weekly cationic column.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/16 STATUS: Completed FY94

TITLE: Attitudes Toward Condom Use Among Adolescent Females

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: CPT Michael J. Christ

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Dillon

KEY WORDS: Condom, Adolescent

Study Objective: To clarify and define the attitudes, knowledge, and sexual behavior regarding condom use among adolescent females in order to identify areas in which counseling and education may reduce the risk of sexually transmitted disease and unwanted pregnancy.

Technical Approach: Adolescent females presenting to our clinic for routine gynecological care and choosing to participate will be asked to complete an anonymous survey to further define their experience with and their attitudes toward condom use. The physician will also obtain information including the patient's age, race, age at onset of sexual activity, number and sex of partners, and history of prior sexually transmitted diseases.

Progress: This study has been completed. There were a total of 200 subjects entered.

Abstract: A significant number of adolescents are sexually active but do not take effective measures to prevent sexually transmitted diseases (STDs) or pregnancy. While condom use is the most effective means of preventing HIV infection or other STDs, little is known about the factors that influence condom use among adolescent females. We hypothesize that at least four factors determine condom use: prior use, complication of prior use, confidence in efficacy, and health beliefs and education. To examine the influence of each of these factors, a 53-item questionnaire was administered to sexually active females presenting consecutively to an adolescent clinic for routine gynecological care. Two hundred adolescents with a median age of 17.0 years (range 14-21) completed the survey. The patients were ethically diverse with 41% (82/200) Caucasian, 26% Hispanic, 17% Black, and 4% Asian. Median age at the time of the first sexual encounter was 15 years (9-20). The median number of lifetime partners was 2 (1-64) with a median of 1 partner (0-10) in the past year. Condom use was reported in 85.4% (175/198) with 21.7% always, 37.9% usually, 25.8% occasionally, and 14.6% never using condoms. Only 47.4% (93/196) had used condoms during the last sexual encounter. Negative experiences, to include pregnancy (6.2%; 12/195), wee reported by 85% of respondents. At least 63% (127/199) of patients reported that condoms were "good" or "excellent" at preventing STDs. Only 54% (108/200) would definitely and 19% would probably use condoms during the next sexual encounter. The intent to use condoms in the future was significantly associated with the frequency of past condom use ($p<0.0001$) and the fear of acquiring HIV infection ($p<0.03$). Other factors examined, such as prior negative experience with condoms, perceived efficacy in prevention of other STDs or pregnancy, or other perceived benefits of condom use, were not significantly predictive of future condom use. These data demonstrate that in adolescent females, past condom use and fear of HIV infection are highly predictive of future condom use. This suggests that early intervention and patient education regarding the proper use of efficacy of condoms may promote consistent condom use in sexually active adolescent females.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/24 STATUS: Terminated FY 94

TITLE: Dietary Treatment of Hypercholesterolemia in Adolescents

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Dec 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne Cuda

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Rupp, MM Beverly

KEY WORDS: Hypercholesterolemia (Adolescent)

Study Objective: To identify whether adolescents are a group that will need more therapy or a modification of the currently recommended therapy for hypercholesterolemia.

Technical Approach: A flyer will be available at the Adolescent Medicine Clinic front desk which will explain the study to interested adolescents and their parents. If an individual is interested in participating, he/she will be given a laboratory slip for a non-fasting serum cholesterol and triglyceride level and will be asked to provide a phone number. If the serum cholesterol is greater than 200 mg/dl, the patient will have a fasting lipid profile. Should the level return at greater than 170 mg/dl but less than 200 mg/dl, the individual will be contacted and asked to repeat the test. If the mean of the two tests is greater than 170 mg/dl, the individual will have a fasting lipid profile. Should the individual persistently show cholesterol levels greater than 170 mg/dl or LDL-cholesterol levels greater than 110 mg/dl, he will be asked to make an appointment with either Dr. Cuda or Dr. Rupp, or to set up a time when he can be counselled by Ms. Beverly.

At the appointment the adolescent will fill out a questionnaire covering age, sex, family history of cardiovascular disease, current address and phone number, and prior diet modification for cardiovascular disease. Weight, height, and blood pressure will also be obtained.

The patient will then be randomized into treatment or non-treatment groups. The treatment group will receive counselling on the Step I diet as recommended by the AHA. The treatment group will be followed up in six months and undergo repeat serum lipid and lipoprotein testing. The non-treatment group will be followed up in six months with repeat blood testing. Should the patient have persistent hypercholesterolemia at follow-up then they will be counselled for the Step I diet and followed clinically.

Progress: Private Investigator PCS'd and study has been Terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/07 STATUS: Completed FY 93

TITLE: Adolescent Risk Factors: Can We Predict the Presence of Activated HPV Oncogenes E6 and E7

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 92 ESTIMATED COMPLETION DATE: May 93

PRINCIPAL INVESTIGATOR: MAJ Suzanne E. Cuda

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Rupp, C Dillon, JD Foley, WF Nauschuetz

KEY WORDS: Adolescent Risk Factors; HPV Oncogenes

Study Objective: To find the incidence of HPV, the incidence of activated HPV oncogenes and identify possible cofactors of activation in our population.

Technical Approach: The pap paddle and cytobrush used in routine gynecological examinations and then disposed of will be tested for HPV and activated oncogenes. The swab used in gonorrhea cultures on males with urethritis will also be tested prior to disposal. Urine samples from males will also be tested prior to disposal. Results will be correlated from data on risk factors normally maintained in charts. 200 female and 50 male patients, ages 13-21 years, will be studied.

Progress: There were 200 subjects entered in this study with no noted adverse reactions. 2 Study was completed in August 1993, but Dr. Dillon, an associate investigator, reported that MAJ Suzanne E. Cuda has the data and is currently in Heidleburg, Germany.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/88 STATUS: Completed FY 94

TITLE: Incidence of Corynebacterium Haemolyticum Pharyngitis in an Adolescent Clinic

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 89 ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: CPT Christoper Dillon

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Weisse

KEY WORDS: Corynebacterium Haemolyticum Pharyngitis, Adolescents

Study Objective: The incidence and seasonal variation of corynebacterium haemolyticum pharyngitis will be determined over a one year period in the Adolescent Clinic at WBAMC.

Technical Approach: All patients (13-20 years of age) presenting to the Adolescent Clinic at WBAMC with a complaint of "sore throat" who receive a throat culture will automatically be included in the study., It will be conducted over a one year period. A checklist of associated signs and symptoms will be used to standardize the information charted on each patient. No additional tests are needed. The throat culturette which would be obtained anyway will be sufficient. In the lab, the culturette will be plated out on the usual blood agar plates, but those from the Adolescent will be marked to be held for 72 hours. Group A beta hemolytic strep can be read at 24 hours (or less), but corynebacterium haemolyticum takes 48-72 hours for adequate growth. those plates with growth suspicious for Corynebacterium haemolyticum will be verified using sugar fermentation techniques.

Patients with a positive culture will be contacted and prescribed a ten day course of erythromycin. (The lab will do sensitivity tests periodically on cultures to determine alternate therapies.) The patients will also be requested to return after treatment for a follow-up throat culture to ascertain eradication of infection. Those who have not responded will be tested for co-incident infectious mononucleosis. Household contacts under age 22 will be requested to also have a throat culture (due to the high incidence of positive results in this population shown in Miller's study).

Those patients identified as having corynebacterium haemolyticum will benefit by treatment which should decrease duration of illness, recurrence of infection, and propagation to others in the household. Risks are minimal. No invasive tests are being done. Erythromycin (250mg four times a day for ten days) is among the safest of antibiotics. (Its main side effect is nausea, which can be minimized by taking it with food.)

Amendment (Jan 93): Added CPT Dillon as new PI (MAJ Weisse became the associate); deleted Martinko and Wittler as associates; changed completion date to Nov 93; changed number of subjects to 1000; updated the DA 5303-R; and changed the funding paragraph.

Progress: Study has been completed. Data collection was completed by CPT Dillon before his PCS move to TAMC in July 1994. There will be no futher entrants into this study.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/15 STATUS: Terminated 94

TITLE: Normal Body Hair Growth Assessment in Hispanic Adolescent Females

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: CPT Christoper Dillon

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Body Hair, Adolescent

Study Objective: Identify normative value of hair growth patterns in Hispanic adolescent females. This, in turn, will assist in determining the need for further workup for hirsutism.

Technical Approach: Retrospective chart review of adolescent females presenting to the adolescent clinic for routine gynecologic exam. Body hair growth patterns will be assessed using the Ferriman and Galloway scale.

Progress: Principal investigator PCS'd to TAMC. Study was not started as principal investigator realized he could not possibly complete the project before his PCS date.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/45 STATUS: Ongoing

TITLE: Up-Front Intensive 6-MP/Methotrexate VS Up-front Alternating Chemotherapy for Acute Lymphoblastic Leukemia in Childhood. POG: 9006

MONITOR (applicable for projects reviewed semi-annually): MAJ Robert Sheffler

START DATE: Jul 93 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Kelly Faucette

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Swaney

KEY WORDS: Methotrexate Leukemia

Study Objective: Our objective is to continue this patient on the randomized trial on which he was started at WRAMC. The objective of this study is to compare, in a randomized trial of children with Acute Lymphoblastic Leukemia (ALL) who are at a higher risk for relapse, the efficacy and toxicity of A: 12 early intensive courses of IV methotrexate (MTX) plus IV 6-mercaptopurine (6-MP) vs. B: 12 early intensive courses of alternating intensive chemotherapy combinations (6-MP/MTX), VM-26/Ara-C, vincristine/ prednisone/ PEG-L-asparaginase/ daunomycin/ Ara-C.

In addition the study is designed to determine if RBC methotrexate/folate levels can be correlated with sites of relapse and event-free survival.

Technical Approach: In summary the protocol is designed to test a potentially more successful method of achieving remission, and maintaining a complete remission until a cure is achieved in a large number of high risk pediatric patients with ALL. Multiagent chemotherapy will be given using standard drugs, but changing the effective oral 6-MP to an IV form to achieve better and more standard drug levels, and drug kinetics, to potentially increase cell kill and effectiveness of therapy. In addition alternating Daunomycin and VM-26, which share some mechanism of cell kill may increase ultimate cell kill and thus survival per the Goldie-Coldman hypothesis.

Progress: Semi-Annual Review (Apr 94): One patient is enrolled in the study with no adverse reactions to report.

Annual Review: We continue with one patient in remission in the WBAMC arm of this protocol. The pateint remains stable with no significant side effects. Should another child be diagnosed with leukemia and fit the criteria for the study, we would anticipate enrolling him/her as well.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 90/06 STATUS: Completed FY94

TITLE: Perceived Susceptibility to Harm During Adolescence

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: COL John D. Foley

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LD Cohn

KEY WORDS: Risk Communication, Probability Expressions, Developmental Limitations, Doctor-Patient Differences

Study Objective: The aim of the proposed research is to determine if teenagers hold exaggerated beliefs about their ability to avoid injury and illness. Such unrealistic optimism has been found to characterize the judgments of adults, and the proposed research seeks to determine its developmental course during early-, middle-, and late-adolescence. Although established procedures exist for assessing unrealistic optimism, these procedures have not been employed with adolescents. The proposed research will fill this gap. In so doing, the research will test the frequent assertion that teenagers overestimate their own invincibility.

A second objective of the research is to determine if unrealistic optimism contributes to the initiation of adolescent substance use, reckless driving, and other health threatening activities. The association between risk-taking and unrealistic optimism will be examined in adolescents in the general population, as well as adolescents who have been hospitalized due to injuries arising from their own risk behaviors. The goal of this comparison is to determine if teenagers who are unsuccessful at avoiding harm-(i.e., hospitalized teens) display the greatest degree of optimistic bias.

A third objective of the research is to determine if unrealistic optimism diminishes when adolescents evaluate dangers for which they are at unique risk. In particular, the study seeks to determine if Hispanic, Black, and White youth show diminished optimism when evaluating the health threats associated with their respective ethnic background (e.g., increased threat of diabetes among Hispanics).

The final objective of the research is to determine if two developmental variables, age and ego development, influence the magnitude of unrealistic optimism displayed by adolescents.

Technical Approach: The details are lengthy and specified in the protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress: All data collection has been completed. An initial article "Adolescents' Misinterpretation of Health Risk" has been accepted for publication by Pediatrics. Two other articles prepared from data collected have yet to be accepted for publication.

Abstract: Objective. To determine if difference exist between adolescents and physicians in their numerical translation of 13 commonly used probability expressions (i.e., possibly, might). Design. Cross-sectional. Setting. Adolescent medicine and pediatric orthopedic outpatient units. Participants. One hundred fifty adolescents and 51 pediatricians, pediatric orthopedic surgeons, and nurses. Measurement. Numerical ratings of the degree of certainty implied by 13 probability expressions (i.e., possibly, probably). Results. Adolescents were significantly more likely than physicians to display comprehension errors, reversing or equating the meaning of terms such as probably/possibly and likely/possibly. Numerical expressions of uncertainty (30% chance) elicited less variability in rating than lexical expressions of uncertainty (i.e.,Possibly) Conclusion. Physicians should avoid using probability expressions such as probably, possibly, and likely when communicating health risks to adolescents.

Numerical expressions of uncertainty may be more effective for conveying the likelihood of an illness than lexical expressions of uncertainty (i.e., probably).

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/91 STATUS: Ongoing

TITLE: Protocol for Determining the Prevalence of Drug Affected Babies in the Military Population

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 89 ESTIMATED COMPLETION DATE: Dec 95

PRINCIPAL INVESTIGATOR: MAJ S Gwynne Geddie

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Meconium, Neonate, Drugs, Cocaine, Marijuana, Newborn, Drug Affected

Study Objective: To determine the prevalence of the use of illicit drugs during pregnancy in a military population.

Technical Approach: This study is to include all pregnant women who present in labor at WBAMC over a 4 month period or 400 patients, and the infants they deliver.

There will be 400 subjects. Two study groups; mothers and infants. A urine drug screen for marijuana, PCP, cocaine and heroin will be done on all subjects. The drug screen is an enzyme immunoassay. This is a test that is not normally done on these type patients. Urine will be collected from all mothers upon admission to labor and delivery, and frozen. All newborn's first void will be collected with a urine bag and frozen. Biweekly both sets of specimens will be sent to toxicology and assigned study identification numbers. The assay will then be performed.

Data will be collected weekly from the toxicology section of the laboratory and analyzed to determine the prevalence of positive drug screens in the mothers and the infants.

Amendment #1 (Sep 90): Added new associate investigators and amended para 7d and 7g.

Amendment #2 (Nov 91): Changed PI to CPT Knight; deleted associate investigators Gordon & Valerie Bell, Howard Oaks & Ingrid Chamales; added LTC Rosa, MAJ Jesse and Dr. Handel as associate investigators. Amendment extended study completion date to Oct 92 and added R.E. Thomason General Hospital (RETGH).

Amendment #3 (Sep 92): Added CPTs Murphy and Maxwell as associates; added another paragraph to status; changed Plan to read: Due to the recently initiated "early discharge" policy for selected newborns at WBAMC, difficulties in obtaining sufficient uncontaminated urine specimens (non-invasively) have arisen and make this source for analysis of illicit drugs impractical. Collection of meconium specimens from newborns at WBAMC is much easier than obtaining uncontaminated urine specimens (non-invasively). WBAMC DCI currently has the technical ability to analyze meconium specimens for illicit drugs and their metabolites; changed 7.d to incorporate previously approved changes (Amendments #1 & #2); amended Duration of Study read: Through October 1992 or until 400 paired materanal urine/neonatal meconium specimens have been obtained; added references (4) and (5).

Progress: Progress has been hampered by the GCMS being out of service for 9 months. It is now back in service and we are going to run samples again. Fifty subjects have been entered with no noted adverse reactions. There has been a change in the estimated completion date from Nov 95 to Dec 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/22 STATUS: Terminated FY 94

TITLE: The Effect of Epidural Anesthesia on Parturient Temperature and Its Relationship to Neonatal Evaluations

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 93 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: CPT Ana C. Hodges

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SW Jesse, GA Meneffee, EJ Bollerup, SG Geddie

KEY WORDS: Epidural Anesthesia; Parturient Temperature

Study Objective: To investigate the effects of epidural analgesia on maternal temperature in labor and subsequently on newborn temperature and outcome, specifically sepsis evaluation and/or treatment.

Technical Approach: Prospective, non-randomized, non-blinded evaluation. All infants will have been vaginally delivered. All patients will be chosen for inclusion based on a calendar time period.
Maternal Groups: I: Controls: Primiparous females, singleton fetus, no epidural or other anesthesia/analgesia.
II: "EPI": Primiparous females, singleton fetus, epidural anesthesia administered in active labor under current WBAMC OB/GYN standard of care. No IV analgesia.
III: "IV": Primiparous females, singleton fetus, active labor, IV analgesia as per WBAMC OB/GYN standard of care.

All infants born to above parturients will be evaluated and treated per current WBAMC/NICU guidelines. Information recorded will include interval temperatures, physical exam status, positive/negative sepsis evaluation and hospital course.

Comparison will be made of parturients' temperatures within and between maternal groups; neonates will be compared for temperature, positivity/negativity of sepsis evaluation and hospital course within and between maternal groups.

Statistical analysis will include ANOVA, which may be used to compare intrapartum temperatures between maternal groups. Student's t-test will be used to compare maternal temperatures at the time of delivery between maternal groups, as well as initial neonatal temperatures between maternal groups. An odds ratio will be used to compare the relative risk of a neonate requiring a sepsis evaluation between maternal groups as it applies to maternal temperature.

Progress: This project has been terminated due to inability to collect necessary data based on current documentation as specified by protocol. Unsure whether modification of protocol would correct problem.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/29 STATUS: Completed FY94

TITLE: Small Bowel Carcinoma in Children

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 93 ESTIMATED COMPLETION DATE: May 94

PRINCIPAL INVESTIGATOR: CPT Ana Hodges

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K Faucette, TM Reyna

KEY WORDS: Bowel Carcinoma

Study Objective: To determine through retrospective use of charts of patients with small intestinal carcinoma, the presentation and results of the varied modalities of treatment. Knowing that the overall numbers of cases are relatively small, it would require a review of multiple centers to accomplish any meaningful study. Additionally, since chemotherapy and radiation therapy are not without significant morbidity in growing and developing children, any study that might safely limit their usage would reduce these complications in this population.

Technical Approach: A retrospective analysis of all cases of small intestinal carcinoma registered within the military tumor registry system will be conducted. The cases will be studied for mode of presentation, demographic data, treatment instituted, outcome, and followup. This will be compared with similar findings in adult literature.

Progress: There has been one subject entered in this study with no noted adverse reactions.
Case report and literature have been completed and undergoing editing prior to submission for publication.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/37 STATUS: Completed FY94

TITLE: Adolescents and Violence: Attitudes in the 90's

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 94 ESTIMATED COMPLETION DATE: Jul 95

PRINCIPAL INVESTIGATOR: CPT Ana Hodges

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SE Spencer, JW Hanks

KEY WORDS: Adolescents, Violence, Attitudes

Study Objective: To determine the attitudes, knowledge, and behaviors among adolescents regarding various areas of risk-taking activity, substance abuse, crime and punishment in order to identify prevalent attitudes and target educational attempts in an effort to reduce violence in our population.

Technical Approach: All adolescents presenting to our clinic for routine care and choosing to participate will be asked to complete an anonymous survey defining their experiences and attitudes concerning violence, crime and punishment. The physician will also obtain information including patient's age, race, religion as well as other epidemiological factors.

Progress: There were 141 questionnaires completed and data collected. Abstract completed and submitted to TriService and Adolescent Medicine meetings. Paper for publication ongoing, expect completion, Spring 1995.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/09 STATUS: Terminated FY94

TITLE: Oral versus Intravenous Antibiotic Therapy for Febrile Urinary Tract Infections

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 92 ESTIMATED COMPLETION DATE: Nov 93

PRINCIPAL INVESTIGATOR: CPT Michael Hunt

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): ML Weisse, AJ Moreno

KEY WORDS: Urinary Tract Infections

Study Objective: To determine whether oral antibiotics are equal in efficacy to intravenous antibiotics in treating febrile UTIs.

Technical Approach: All patients with febrile UTI's will be admitted to the pediatric inpatient service. After parental consent, the patient will be assigned randomly (table of random numbers) to oral or intravenous antibiotic therapy. The oral antibiotic is augmentin dosed 30-40 mg/kg/day div q 8 hours. The intravenous antibiotics are ampicillin 100mg/kg/day div q 6 hours and gentamicin 6-7.5 mg/kg/day div q 8 hours. The temperature of the patient will be followed until afebrile for twenty-four hours, and the urine until sterile. The urine and organism will be saved for study.

Amendment (IRB Jan 93): (1) Added COL Moreno as associate; (2) added "To ensure patient safety, each patient will have a urinary ultrasonogram and a Tc-DMSA (Tc- dimercapto-succinic acid) renal scan after admission to the ward." to end of STUDY DESIGN; (3) amended ANALYSIS of RISKS and BENEFITS to SUBJECTS and RISKS to those CONDUCTING RESEARCH to read: All patients will benefit by having the UTI treated under continuous observation by the Pediatric staff and house staff, laboratory support by a medical center, and the rapid availability of urological consult if necessary. A urinary ultrasound will be done to rule out the possibility of urinary obstruction; (4) amended FOLLOW-UP PROCEDURES to read: Each patient will have a renal ultra sonogram performed by the radiology department to rule out obstruction within eighteen hours of admission. A Tc-DMSA will be performed by the Nuclear Medicine Department to assess kidney involvement. Urine cultures will be repeated after completion of antibiotic therapy, and the patient will have follow up with house staff continuity clinics in consultation with Pediatric Infectious Disease Department; (5) amended FUNDING IMPLICATIONS to read $3700.00 (Nuclear Imaging); $1000.00 (TDY for presentation at scientific/clinical meetings); $300.00 (Reprints); TOTAL $5000.00.

Progress: Principal investigator PCS'd so protocol has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/49 STATUS: Terminated FY 94

TITLE: A Comparison Study of Midazolam and Pentobarbital Versus Pentobarbital Alone in the Effective Sedation of Children for Non-Invasive Imaging

MONITOR (applicable for projects reviewed semi-annually): MAJ Steve Rubin

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Aug 94

PRINCIPAL INVESTIGATOR: CPT Michelle B. Kravitz

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): K Faucette

KEY WORDS: Midazolam, Pentobarbital, Sedation, Children

Study Objectives: To compare the use of midazolam combined with pentobarbital vs the use of pentobarbital alone to sedate children for non-invasive imaging.

Technical Approach: This will be a prospective, double-blinded comparison study. All patients admitted for sedation between September 1993 and August 1994 who do not meet the exclusion criteria (see 6g) will be enrolled. The patient's age and weight will be entered in the computer and pharmacist alerted that the patient is a sedation study participant. The pharmacist will then send a darkened syringe containing either 0.1mg/kg midazolam or an equal volume of normal saline. The contents of the syringe will be injected intravenously following an initial dose of 2mg/kg of pentobarbital. An additional dose of pentobarbital will then be added (in increments of 25mg or 1mg/kg, whichever is less) until adequate sedation is achieved. Pentobarbital is given initially to all patients to best blind the study. Mixing of the two agents in one syringe cannot be done secondary to incompatibility and precipitation of versed with pentobarbital.

The sedating physician will fill out a questionnaire on each patient sedated by study protocol. This will include the following: 1)Name of patient.

2)Age of patient.

3)Medications patient takes at home.

4)Prior history of failed sedation and if so, drugs used to sedate at that time.

5)Imaging study needed/why study needed.

6)Study drug number (assigned by pharmacy to allow us to find out which drugs were used to sedate patient).

7)Dose of additional pentobarbital required.

8)Whether repeat sedation was required (defined as additional pentobarbital or other agent administered after pt left ward). Any mitigating factors, such as delay by MRI or CT in commencing study, will also be noted here.

9)Time to onset of sleep.

10)Duration of sedation.

11)Length of time until awake enough for discharge.

12)Side effects noted.

Progress: Semi-Annual Review (Apr 94): The study started late secondary to administrative details, but officially work began in January 1994. It is mostly geared for MRI, so the fact that acceptable monitoring for IV sedation in MRI only arrived March 7, 1994 decreased the numbers of patients dramatically. Also, one patient whose mother had given consent for the study had his MRI postponed because of MRI malfunction (not the monitoring).
All 10 patients enrolled have been successfully sedated and awakened without complications.

Anecdotally, one parent, after hearing about the study, refused to participate because he wanted to make sure his son was not in the control group. He requested the versed pentobarbital combination because his son had become very agitated with pentobarbital alone last year. His father stated that he did much better with the combination (ativan was given first). While he had some mild agitation, this was much less dramatic and more easily controlled. We would like to continue at present doses for 1-2 more months and if review of data then still shows no significant difference between groups, we would like to increased the versed dose to .1 mg/kg. If such is the case, an amendment concerning dosage will be submitted.

Annual Review: Eleven subjects were entered with no noted adverse reactions. This study was terminated in June 1994 due to lack of cooperation of housestaff in recruiting patients for study and improper administration of medications/incomplete data collection on the few patients who were enrolled. All patients enrolled were successfully sedated - both placebo and versed. No difference seen between patients.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/52 STATUS: Terminated FY94

TITLE: Retrospective Comparison of the Electrocardiograms of Subjects Having Sickle Cell Trait and Controls

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Sep 93 ESTIMATED COMPLETION DATE: Mar 94

PRINCIPAL INVESTIGATOR: COL William Pearl

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): IM Weisman

KEY WORDS: Electrocardiogram, Sickle Cell Trait

Study Objective: To determine whether subjects with sickle cell trait have different electrocardiograms than controls.

Technical Approach: Review of electrocardiograms already obtained on subjects having sickle cell trait and controls.

Progress: The protocol has been terminated because the principal investigator left.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/43 STATUS: Ongoing

TITLE: A Phase III Randomized, Double-Blind, Placebo-Controlled Trial of Monthly RespiGam (RSVIG-IV) Infusions for Reduction of the Rate of RSV Hospitalization in Premature Infants with Bronchopulmonary Dysplasia

MONITOR (applicable for projects reviewed semi-annually): MAJ William Raszka

START DATE: Sep 94 ESTIMATED COMPLETION DATE: June 95

PRINCIPAL INVESTIGATOR: MAJ Bruce E. Pichoff

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Rettke, S Lindow, S Remich, C Moreno, A Varner

KEY WORDS: RespiGam, Infants Bronchopulmonary Dysplasia

Study Objective: The primary objective of this study is to determine the safety and efficacy of monthly RespiGam prophylaxis in reducing the rate of RSV hospitalization in premature infants and infants with BPD. Secondary objectives include determining the effect of monthly RespiGam prophylaxis among study participants on the following hospital parameters: (1) total days of RSV-related hospital stay, (2) supplemental oxygen requirement and oxygen saturation, (3) WHO LRI score, (4) frequency of ICU care and total days of ICU stay, and (5) frequency and total days of mechanical ventilation.

Technical Approach: See basic protocol (pages 14-37). There will be no deviations by WBAMC from the basic plan.

Progress: This study has just started, therefore, no progress has been reported.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/40 STATUS: Terminated FY 94

TITLE: Measles Immunity in New Housestaff

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jun 91 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): M Schydlower

KEY WORDS: Measles Immunity, Medical Interns

Study Objective: To determine the prevalence of immunity to measles in a group of health care workers, who are also young adults; to ensure immunity of new housestaff and to be cost-effective in immunizing new housestaff.

Technical Approach: A questionnaire will be administered to newly arriving interns at WBAMC to determine their past history with respect to measles infection. Immunization records will be reviewed to assess the number and timing of immunizations to measles. Sera will be drawn on each new intern for determination of individual immunity using ELISA.

Progress: This protocol has been terminated by principal investigator's choice.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/25 STATUS: Ongoing

TITLE: Prevalence of Hypogammaglobulinemia in Children with Recurrent/Persistent Otitis Media

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Jul 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Hypogammaglobulinemia, Igb Deficiency

Study Objective: To determine the prevalence and extent of IgG deficiency in otitis prone children.

Technical Approach: Patients meeting the criteria below will have the study explained to them, and after informed consent is obtained, blood will be drawn for 1) complete blood count with differential, 2) quantitative immunoglobulin A, E, G, M, and 3) immunoglobulin G subclasses. If patient has an acute infection with fever at the time of clinic visit, the tests will be drawn at the next visit that the patient is seen and the acute infection is resolved.

Children 1 to 10 years of age presenting to pediatric clinic with history of 3 episodes of acute otitis media in the preceding 6 months, or duration of serous effusions greater than or equal to 3 months after an episode of acute otitis media, will comprise the study population.

All patients will be followed by the principal investigator and the lab results explained. Treatment options/considerations based on clinical and laboratory evaluations will be discussed and most appropriate and acceptable therapy will be implemented.

Progress: This study was initiated by Dr. M. Weisse. I do not know where the records and the data are located. I will consult with the original PI to discuss the possibility of continuing this protocol.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/17 STATUS: Completed FY 94

TITLE: Delayed Type Hypersensitivity Skin Testing in Human Immunodeficiency Infected Children

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Apr 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): ML Robb

KEY WORDS: Skin Testing, HIV, Children

Study Objective: The objective of this study will be threefold. First we hope to determine if HIV infected infants and children develop apppropriate DTH responses. If patients are able to develop appropriate cellular immune responses, we would like to determine how long those responses persist. Finally, we will determine the relationship between DTH responses and evidence of clinical immune suppression.

Technical Approach: The study will be a retrospective chart review of DTH skin testing data that has been gathered in a prospective fashion in HIV infected children enrolled in a natural history study. The patients age, immunization status, clinical stage (1987 CDC classification system), antiretroviral use, HIV risk factors, and CD4+ lymphocyte populations will be analyzed. In addition, the mean size of the induration associated with each DTH antigen will be analyzed. Statistical analysis will be with Chi-square.

Progress: The study has been completed. There were 102 subjects entered with no noted adverse reactions.

Abstract: Background: Although DTH Skin testing to recall antigens has been used to clinically stage adults with HIV disease, little is known about the ability of HIV+ children to mount an immune response to intradermally placed antigen. Methods: The DTH responses of HIV+ children who survived the first year of life were prospectively evaluated. On a yearly basis, 0.1 cc volumes of 6 to 7 antigens were intradermally injected on the patient's forearm and the mean diameter of the induration at 48 hours measured. Antigens tested included dilutions of stock concentrations of PPD (5 TU), mumps ST (1:20), tetanus toxoid (1:10 and 1:100), trichophyton (1:30), and C albicans (1:10 and 1:100). Patients were considered anergic if they had no response and partially anergic if they had only one cutaneous response greater than 4 mm to any antigen. Results: 61 DTH panels from 26 ethnically diverse, appropriately immunized patients (16 male) were evaluated. Mean age of the patients during the study was 84 months (range 8.5 - 156). Risk factors for HIV infection included perinatal exposure (16), hemophilia (8), and transfusion (2). Patients were asymptomatic (1987 CDC stage P1) during 42/61 DTH determinations. Patients demonstrated DTH responses to all antigens tested except PPD. No adverse reactions were noted. Tetanus toxoid (1:100), and trichophyton had the fewest number of responses (10/46 and 17/59) and the smallest mean size of induration in responders (8.0 and 8.5 mm). Mumps and C albicans 1:10 had the greatest number of reactions (44/61 and 39/50) and the largest mean size of induration in responders (11.4 and 16.9 mm). Only 2/42 asymptomatic patients demonstrated complete anergy compared to 5/19 symptomatic patients ($p<0.02$). Anergy was associated with low CD4%. Mean CD4% in anergic patients was 7.8% compared to 26.8% in patients with normal DTH responses ($p<0.01$). Conclusion: HIV+ children surviving the first year of life exhibit appropriate in vivo cellular immune responses for a longer duration of time than expected and that DTH reactions may be useful as a predictor of disease progression in HIV+ pediatric patients.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/21 STATUS: Ongoing

TITLE: Immunoregulation and Pathogenesis of Symptomatic, Primary HIV-1 Infection

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Jan 97

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): ML Robb

KEY WORDS: Immunoregulation, Pathogenesis, HIV-1

Study Objective: The objective of this study will be to determine and follow the genotypic expression of the HIV from the earliest moments of infection and the very specific patient immune response to the evolving genotypic expression. We also hope to characterize viral burden and correlate viral burden with genotypic expression, specific immune responses, and clinical disease. This will be important as it is not known which factors (viral specific or host specific) that lead to the expression of HIV virus during the acute retroviral syndrome and the ability of the host's immune response to at least initially control the viral infection. A better understanding of this mechanism may lead to effective immunotherapeutic approaches to this disease.
The role of the WBAMC PI will be in identifying patients with acute retroviral syndrome and following the patients clinically. WBAMC (the PI) will be responsible for blood drawing and shipment of clinical specimens.

Technical Approach: The study will be prospective, natural history. Details are lengthy and are specified in the original protocol. Copies are on file at DCI.

NOTE: This is a Tri-Service protocol which originated at Walter Reed Army Medical Center and was approved at the Human Subject Research Review Board meeting in May 93.
Progress: A single patient from WBAMC has been enrolled. There were no complications to her blood draws. Her virus is an unusual strain of the typical North Americn Clade.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/28 STATUS: Completed FY 94

TITLE: Influenza Vaccination Rates among Pediatric Health Care Providers

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 94 ESTIMATED COMPLETION DATE: Sep 94

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): C Westbrook

KEY WORDS: Influenza Vaccination Rates

Study Objective: The objective of this study will be to determine the vaccination rates among all health care providers in El Paso who see children on a regular basis. The vaccination rates among the following, non-exclusive groups will be evaluated: 1)military 2)civilian hospital-based 3)civilian office-based 4)generalists 5)specialists 6)residents 7)faculty 8)American Board of Pediatrics certified 9)not ABP certified. The reasons for non-compliance with either Army regulations or vaccination recommendations will be ascertained.

Technical Approach: Questionnaire

Progress: The study has been completed. There were 117 subjects entered with no noted adverse reactions.

Abstract: Background: Yearly influenza immunization is recommended for all PHCP who have contact with high-risk children. Objective: To assess 1) the percentage of PHCP in an entire medical community that had been immunized with influenza vaccine at the onset or during the 1993-1994 winter season and 2) reasons for non-compliance with influenza immunization guidelines. Methods: A five-item questionnaire was individually administered to all PHCP identified by registry at tow residency programs, The El Paso Pediatric Society, and the Yellow Pages. Nurses, other than nurse practitioners, were excluded from the study. All hospitals with in-patient pediatric services were surveyed to determine local PHCP influenza immunization requirements. Results: Of the 119 PHCP identified, 117 completed the survey (99%). PHCP consisted of community-based private practitioners (34/117; 29%) and hospital-based practitioner 83;71%) who were evenly distributed between tow residency programs. Board certified pediatricians (33/117; 29%), pediatric sub-specialists (28%), and residents (28%) accounted for the bulk of the respondents. One hospital (associated with a residency program) required influenza immunization, one highly recommended immunization, while the rest had no policy regarding influenza immunization in PHCP. Only 67% (79/117) of PHCP had been immunized with influenza vaccine. No difference was detected in the compliance rates among community or hospital-based practitioners, pediatric sub-specialists, general pediatric practitioners, residents, residency programs, or hospitals. Hospital policy regarding influenza immunization did not influence the compliance rate. Overall and in all groups of PHCP, the most common reasons for non-compliance were "forgot/didn't have time" (21/35, 60%) followed by "don't like shots" (20%) and "don't believe it is efficacious" (11%). Conclusions: One third of PHCP, regardless of training or practice, are not compliant with current influenza immunization guidelines. Minimizing the risk of influenza disease in high-risk pediatric patients will require PHCP education regarding influenza vaccine indications as wall as a surveillance system to monitor PHCP compliance with both national immunization guidelines and local infection control requirements.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/35 STATUS: Ongoing

TITLE: Knowledge of Immunization Practices Among Pediatric Health Care Providers in Medical Centers

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 95 ESTIMATED COMPLETION DATE: Feb 95

PRINCIPAL INVESTIGATOR: MAJ William Raszka

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Immunization, Health Care Providers

Study Objective:

1) To determine the body of knowledge regarding current pediatric immunization practices that pediatric housestaff have at each level of training.

2) To determine the body of knowledge regarding current pediatric immunization practices that pediatric staff have by type of specialty.

3) To determine if housestaff from military programs are any different from civilian programs.

Technical Approach: Survey using a validated survey form. The survey was validated by administering it to pediatric infectious disease specialists and general pediatricians not participating in the study.

Progress: There has been 200 subjects entered in this study with no noted adverse reactions. Eight centers completed the survey. Data has been entered and has not been analyzed. The estimated completion date has been changed from Jan 95 to Feb 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/12 STATUS: Completed FY 94

TITLE: Incidence of Occult Urethral Human Papilloma Virus (HPV) Infection in Sexually Active Adolescent Males

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 92 ESTIMATED COMPLETION DATE: Feb 94

PRINCIPAL INVESTIGATOR: MAJ Richard Rupp

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Cuda, W Nauschuetz

KEY WORDS: HPV (Adolescent)

Study Objective: To find the incidence of HPV infections in sexually active adolescent males and to possibly explore the feasibility of screening males for occult disease.

Technical Approach: The study will include approximately 100 males presenting to the Troop Clinic or the Adolescent Clinic, who are found on routine health screening to be sexually active or with complaints secondary to sexual activity. Sexually active males choosing to participate will be asked to provide a first morning urine. Participating sexually active males presenting with urethritis also will have an additional urethral swab done. These specimens will be tested using HPV DNA detection techniques. Virapap and Viratype kits are sensitive to as little as 102- 103 viral particles which can be as few as 100-200 infected cells. The physician will obtain information including patient's age, age at onset of sexual activity, race, prior STDs, number and sex of partners, and whether the patient is circumcised. All patients will have a follow-up appointment to be counselled on positive and negative results. The subjects will be offered testing for other STDs (i.e., HIV, RPR, gonorrhea, chlamydia).

The data should help delineate the epidemiology of occult HPV in sexually active adolescent males. Condylomata are extremely rare in males of this age. With the high rates of infection found in adolescent females it is likely there is a high rate of occult HPV infections in males. From this data, it may be possible to make conclusions about the usefulness of male HPV screening tests. Knowledgeable about his HPV status, a patient will be able to make informed decisions about risky sexual behavior that may protect him and his partners.

Progress: Specimen collection is complete, with a total of seventy-five. We are awaiting results from DNA/PCR Lab which will be done outside WBAMC, due to DCI staffing constraints. Principal investigator has PCSed.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/55 STATUS: Ongoing

TITLE: Parents Opinions about Disorders of Vigilance in their Children with Attention Deficit Disorder

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 91 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: LTC Robert Sayers

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AW Atkinson

KEY WORDS: Primary Disorder of Vigilance (PDV), Attention Deficit Hyperactivity Disorder

Study Objective: Through the use of a parent questionnaire, determine the incidence of symptoms of Primary Disorder of Vigilance (PDV) in a population previously diagnosed with Attention Deficit Disorder (ADD) or being evaluated for ADD. Furthermore, this project will seek to differentiate this symptom cluster (PDV) as either a unique diagnosis or a subtype of ADD.

Technical Approach: The Developmental Pediatric Clinic at WBAMC follows approximately 180 patients with the diagnosis of ADD. Patients who are taking medication for ADD are seen in clinic at least every three months and parents come in for a brief interview on progress and refill every month. During one of these routine follow-ups, the parent will be asked to complete a questionnaire which addresses the major criteria for PDV for both the child and his/her parents. These criteria are taken directly from the article "Primary disorder of vigilance: A novel restlessness, and sleepiness" by Weinberg describing this "new" disorder.

Progress: Number of subjects entered in the study is 120. At this time data collection has been completed but data analysis is still ongoing.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/41 STATUS: Ongoing

TITLE: Hepatitis B Virus Immunization Rates Among Adolescents

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 94 ESTIMATED COMPLETION DATE: Mar 95

PRINCIPAL INVESTIGATOR: CPT Steven E. Spencer

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Raszka

KEY WORDS: Hepatitis B, Innunization, Adolescnets

Study Objectives: To determine the HBV immunization rate among adolescents seen at WBAMC with both high and low risk behaviors for acquiring HBV infection.

Technical Approach: Medical records of adolescent patients seen at the WBAMC adolescent clinic will be reviewed. Information recorded will include evidence of sexual activity (as noted in chart), immunization record, last name, family member prefix, and last four digits of sponsor's social security number. This is to ensure that there is no duplication of chart reviews. All identifiers will be purged after data collection and analysis.

Progress: This study has just started, therefore, no progress has been reported.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/59 STATUS: Completed FY 94

TITLE: Emergency Use of Erwinia Asparaginase for Treatment of Acute Lymphocytic Leukemia (Patient C.H. 3759)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: Dr. Jerry Swaney

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Lymphocytic Leukemia

Study Objective: To increase the response rate of acture lymphoblastic leukemia (ALL).

Technical Approach: Patient developed an allergic reaction to asparaginase produced by Escherischia coli. Erwinia asparaginase is to be substituted for the E. coli-based produce for the remainder of the protocol (18 of 20 doses).

Progress: This study has been completed. There was 1 subject entered in the study with no noted reactions. Patient CH 3759 presented in bone marrow relapse of his acute lymphocytes leukemia 5 Oct 94 with 61% leukemia cells in his bone marrow. He received 4 injections of Erwina L-asparaginase on 7, 13, 19, 27 October 94. He attained a partial remision with 15% leukemia cells on 3 Nov 94. There were no noted reactions. Therapeutic goals partially attained 61% to 15%.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/62 STATUS: Terminated FY 94

TITLE: Medical Experience of The Third Armored Cavalry Regiment During Operations Desert Shield and Desert Storm

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 91 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: MAJ Glenn M. Wasserman

DEPARTMENT: Pediatrics FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Martin, H Oaks, H McAdoo, R Harvey, B Merrill, C Hyams

KEY WORDS: Gulf Crisis, Persian Gulf Crisis, Military Medicine

Study Objective: The aim of this project is to review and analyze the military, medical experience of first and second echelon medical units attached to a forward line unit (The Third Armored Cavalry Regiment) during Operations Desert Shield and Desert Storm.

Technical Approach: Data will be obtained primarily from retrospective review of preventive medicine disease surveillance data, self-completed questionnaires (Fourth Squadron), stool culture and ova & parasite analysis, and after action reports. There will also be anecdotal reports and data from the medical troop commander, dentist, acting psychiatrist and a physician assistant.

Progress: This study has been terminated because the investigators have left WBAMC, unknown status of project/study.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/07 STATUS: Ongoing

TITLE: Clinical Comparability of Two Once-Daily Forms of Diltiazem: Effect of Substitution on Blood-Pressure Control & Resource Utilization

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: MAJ John D. Grabenstein

DEPARTMENT: Pharmacy FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Stanley, RP Potyk

KEY WORDS: Diltiazem

Study Objective: To assess the comparability of clinical effects of CardizemR CD (Marion Merrill Dow Inc., Prescription Products Division, Kansas City, MO 64114) and Dilacor XRTM (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA 19426) in the treatment of hypertension. The Food & Drug Administration has already found evidence of the safety and efficacy of these two dosage forms for this indication.

Technical Approach: Retrospective analysis of patient records (medical records and/or convenience charts) to determine blood pressures during the course of routine medical practice, at medical treatment facilities that have already switched from CardizemR CD to Dilacor XRTM at the direction of the MTF's Pharmacy & Therapeutics (P&T) Committee.

Progress: Data collection has been completed and sent to MAJ John D. Grabenstein at Health Services Command. He will complete the data form other HSF's and publish his report from the results. There has been a change of principal investigator from Pharm D Ron Grosserode to MAJ John D. Grabenstein.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/38 STATUS: Ongoing

TITLE: T-lymphocyte (CD4) counts in patients with diagnosed tuberculosis or other mycobacterial disease who are not infected with the Human Immunodeficiency Virus.

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 94 ESTIMATED COMPLETION DATE: Nov 95

PRINCIPAL INVESTIGATOR: COL Arthur Morton

DEPARTMENT: Preventive Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): R Lundy, MA Escobedo, P Frank

KEY WORDS: T-Lymphocyte Counts, Tuberculosis Mycobacterial

Study Objective: (1) If T-lymphocyte (CD4) cell counts are depressed in patients with mycobacterial disease.

(2) If T-lymphocyte (CD4) cell counts predict treatment success in patients with mycobacterial disease.

Technical Approach:

(1) Criteria for initial enrollment of subjects:

(a) Anti-tuberculosis drug naive

(b) Mycobacterial disease suspected because of a "positive" acid-fast smear of a clinical specimen

(c) Anti-Human Immunodeficiency Virus drug naive.

(d) Patients who present at the El Paso Health and Environmental District or at WBAMC for care.

(2) The initial evaluation will include the following:

(a) A specially designed questionnaire which requests information about: Name, social security number (or another number used for tracking purposes), age, sex, ethnic origin, country of birth, months of residence outside of the U.S., months of residence in the U.S.; history of cough, fever, sweats, weight loss, hemoptysis: prior tuberculosis treatment: IPT, BCG, multiple drug therapy; and AIDS risk factors: multiple sex partners, sex with men, IVDU, frequent blood transfusions, tissue transplants; and other immunosuppressing factors: end-stage renal disease (dialysis), diabetes mellitus (uncontrolled, insulin dependent, or non-insulin dependent), low body weight (less than 80% of ideal), previous partial or complete gastrectomy, regular alcohol use, regular steroid use, cancer, leukemia, cancer chemotherapy, cancer radiation therapy, or regular cyclosporin use.

(b) A serum HIV antibody test.

(c) Sputum or other clinical specimens for culture and sensitivity at days 0,1,2, 30, 90, and 180.

(d) A single Posterior-Anterior x-ray study of the chest will be done at day 0 and will be interpreted by the principal investigator. Each study will be classified into one or more of the following categories:

[(1)] No evidence of past or present tuberculosis.

[(2)] Evidence of healed primary tuberculosis (Ghon lesions or calcified hilar lymph nodes).

[(3)] Infiltrates associated with hilar adenopathy suggestive of an active infectious process consistent with a diagnosis of non-cavitary pulmonary tuberculosis, mycobacterioses, or Pneumocystis Caranii pneumonia.

[(4)] Cavitation consistent with a diagnosis of active pulmonary tuberculosis.

[(5)] Pleural thickening with or without pleural effusion consistent with a diagnosis of pleural tuberculosis.

[(6)] Multiple lesions consistent with a diagnosis of miliary tuberculosis.

[(7)] Other significant abnormalities of the lung which may or may not be associated with tuberculosis.

[(8)] No evidence of chronic obstructive lung disease (COLD).

[(9)] Generalized pulmonary congestion consistent with a history of smoking or other chronic inflammatory lung diseases.

[(10)] Increased lung volume consistent with a diagnosis of early COLD.

[(11)] Increased lung volume with decreased markings consistent with a diagnosis of moderately advanced COLD.

[(12)] Severely increased lung volume, decreased markings, and bleb formation suggestive of advanced COLD.

(e) Each film will also be interpreted by a radiologist for evidence of other pulmonary abnormalities such as lung cancer, enlarged heart, degenerative changes in the thoracic spine, etc.

(f) A tuberculin skin test by the Mantoux method using 5 tuberculin units (0.1 ml.) of Purified Protein Derivative (PPD).

(g) A physical examination which will include measure-ment of height and weight, examination for and evaluation of a scar suggestive of BCG vaccination and for lymphadenopathy.

(h) A complete blood count.

(i) A Westergren Erythrocyte Sedimentation Rate.

(j) A serum ALT (SGOT) test.

(3) A T-lymphocyte (CD4) cell count below 400 cells per cubic millimeter will be considered to be evidence of a significantly depressed count. These patients will be referred to physicians of their choice for further evaluation.

(4) This study design parallels the routine evaluation done by physicians when evaluating patients for evidence of disease caused by the various members of the family Mcobacterium. Additional studies not normally included in the routine evaluation will include the demographic and historical information questionnaire, a T-lymphocyte (CD4) cell count and a HIV test. All patients will be re-evaluated at 30, 90, and 180 days. At the time

of the subsequent evaluations, the T-lymphocyte (CD4) cell count, HIV test, and sputum or other clinical specimens will be obtained for direct microscopic examination for acid fast bacilli and culture will be repeated.

(5) Since there is a long lead time required to obtain mycobacterial culture results and since there is a 6 week to 6 month "window" period between the time of HIV infection and a "positive" HIV serum antibody test, all patients suspected of having a disease caused by a member of the Mycobacterium family will be eligible for initial enrollment. Subjects who are subsequently found to be infected with HIV or who do not receive a final clinical diagnosis of mycobacterial disease will be excluded later.

Progress: Study is anticipated to start in November 1994. The estimated completion date is one year from start date, November 1995. Associate investigator K. Pearl has been deleted and P. Frank added.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/10 STATUS: Completed FY94

TITLE: Assessment of Risk Factors for HIV Infections Among Active Duty U.S. Army Personnel with Documented Recent HIV-Antibody Seroconversion

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 91 ESTIMATED COMPLETION DATE: Jan 96

PRINCIPAL INVESTIGATOR: Karlyn K. Pearl

DEPARTMENT: Preventive Medicine FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): AR Morton; H Rodriguez

KEY WORDS: HIV, Seroconversion

Study Objective: To assess demographic and behavioral determinants associated with new HIV infections. Incident cases are the only population which allow us to investigate important features of the current HIV infection epidemic. Risk factors and their relative significance as determinants of HIV infection will be assessed by comparing medical, demographic, and behavioral histories of active duty personnel recently infected with HIV with histories of individuals who have not seroconverted over a similar time period.

Technical Approach: The study will be conducted using a case-control design. A case will be defined on the basis of HIV-Ab seroconversion (positive Western blot in duplicate). Controls will be randomly selected HIV-Ab negative active duty personnel at the same posts where cases occur, and will be matched to each case on: Age (+/- 2 yrs), race/ethnicity, grade category (junior enlisted, senior enlisted, officer), and length of service in the Army. Two controls will be recruited for each case. Controls must have been tested negative for HIV-AB no earlier than three months before the positive test date of their matched case. Based upon standard methods for determining required sample sizes in a case-control study and the expected number of HIV-AB seroconverters, a 2-year study period is anticipated. All active duty personnel with confirmed HIV-Ab seroconversion will be eligible for inclusion in this study. Cases will be identified each month by review of the USAHDS data base. Physicians in charge of the HIV testing and evaluation programs at posts from which cases are reported will be contacted by WRAIR and asked to invite incident cases to participate in this study. This study is designed to ensure strict confidentiality. All links between name, social security number, or other identification and study numbers are destroyed after the interviews are completed at the study site.

Progress: The study has been completed. There were 16 subjects entered with no noted adverse reactions.

Abstract: Thorough investigation of documented recent infections with HIV (incident cases) is the best way to evaluate risk factors associated with the current HIV infection epidemic, and is important not only to determine any changes in the epidemiology of HIV, but also to target preventive interventions. In addition, the use of a case-control design that is anonymous and confidential is critical for valid risk assessments in these settings. To meet these objectives, the HIV Seroconverted Risk Factor Study (HSRF) was initiated in June 1989.
This case-control study was conducted at 22 Army posts throughout the continental United States. Cases were active duty Army men who seroconverted between July 1986 and December 1991. Controls were HIV-Ab negative soldiers matched to cases on age, race/ethnicity, length of military service, rank and current post. The structured interviews were conducted by civilian interviewers provided by the Centers for Disease Control. The interview elicited information on sex behaviors, injecting drug use and other risks for HIV infection during the interval beginning 6 months prior to the last negative antibody test and extending until the first positive test date for the cases, (median interval = 23 months). Controls were questioned about risk behaviors occurring during the same interval as their matched cases. Stringent procedures were designed to maintain the confidentiality and anonymity of study subjects. As of June 1992, 257 interviews have been completed. Preliminary results from this study

showed that 45% of the cases and no controls reported having sex with men, (Of the cases that reported having sex with men, 69% were bisexual). One case and 2 controls reported using IV drugs. 54% of the cases and 98% of controls never used IV drugs and reported having sex only with women. Among the heterosexual respondents, significant increased risk of infection were found with increasing numbers of partners reported in the interval [Odds Ratio (OR) = 5.8 (95% CI = 2.1 - 16.0) for 6+ partners, relative to 1 partner]; with increasing numbers of partners where sex occurred on the first encounter [OR = 6.8 (95% CI = 2.7 - 17.4) for 3+ times, relative to none];with increasing numbers of non-steady partners (sex less than 10 times with the partner during the interval) [OR = 7.0 (95% CI = 2.7 - 18.2) for 3+ non-steady partners, relative to none]; and with increasing number of prostitutes during the interval or with partners who had multiple sex partners, [OR =3.3 (95% CI = 1.3 - 8.2) for 2+ partners, relative to none]. Thus, this study identified several risk behaviors that impart substantial risk for HIV infection. Moreover, these findings were consistent with those published in other studies.

The HIV epidemic remains a critical public heath problem for military as well as civilian populations. For this reason, we believe it is very important to continue to evaluate behavioral and biologic determinants of HIV seroconvesion among active duty men and women in the Department of Defense.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 87/71A STATUS: Terminated FY 94

TITLE: Emergency Procedures Laboratory (Carpine Model)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 87 ESTIMATED COMPLETION DATE: Indefinate

PRINCIPAL INVESTIGATOR: MAJ Ronald Liss

DEPARTMENT: PCCM FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Emergency Procedures Laboratory

Study Objective: To train accredited physicians who are not dealing with emergencies on a day-to-day basis, but may be called upon to perform this function. The goat model will simulate the human emergency patient.

Technical Approach: Cricothyroidotomy, venous cutdown, chest trauma management, and peritoneal lavage procedures will be accomplished in accordance with training manuals for each procedure.

Progress: Principal investigator has been reassigned so study has been terminated.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/19A STATUS: Terminated FY 94

TITLE: Emergency Life Support Training for Paramedics in the Small Ruminant (Ovine or Caprine) Animal Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Ronald Liss

DEPARTMENT: PCCM FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Emergency Life Support

Study Objective: This training will enhance the paramedics' capabilities of administering emergency lifesaving procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest trauma management.

Technical Approach: The emergency life support training program is designed for paramedics who are primarily responsible for providing first echelon care to the critically injured patient. Procedures taught will be according to the American College of Surgeons (ACS) Committee's Advanced Trauma Life Support Course. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations. Students then rotate through animal laboratories associated with the lecture content previously presented. The animal laboratory allows the student to observe and practice to proficiency those life-saving skills necessary in the initial management and stabilization of the trauma patient. The animal laboratory is approximately 2-3 hours per cycle. Each animal station will consist of one instructor and four to five students.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Principal Investigator has PCS'd so protocol has been terminated. No reponse from C, EMS.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/50 STATUS: Ongoing

TITLE: The Application of Civilian Pre-Authorization Standards to Inpatient Admissions in a Military Treatment Facility

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jul 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: CPT Ronald Szyjkowski

DEPARTMENT: Region FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): LA Popejoy, JJ James

KEY WORDS: Pre-Authorization Standards, Inpatients Admissions

Study Objective: To disprove the hypothesis that civilian healthcare industry pre-authorization program can be effectively applied in a military treatment facility to reduce inpatient expense.

Technical Approach:
Phase I: A study of a small sampling of previously admitted patients. Outpatient chart information on randomly selected cases will be evaluated by experienced civilian peer review nurses using Interqual screening criteria. Subsequently, civilian practicing specialists will review copies of the entire inpatients chart of the same admission episodes.

Phase II: The same peer review evaluation and subsequent physician review of the inpatient chart on concurrent, contemporary admissions. The sample size is estimated at approximately 25 admissions from each of the major inpatient departments.

Phase III: Peer review nurse evaluation for pre-authorization approval of 100% of admissions during a 3-4 month period of time and selective physician review of inpatient charts of these same admissions. A coincident training and education module for providers will be instituted.

Progress: There were 3,800 subjects entered. Patient record review is the remaining data piece of data needed to be collected. Expected completion of data collection on 1 Oct 94 and analysis on 1 Nov 94. There has been a change of principal investigator from COL Lou A. Popejoy to CPT Ronald Szyjkowski.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/17A STATUS: Terminated FY 94

TITLE: The Prevention of Pigmented Gallstones with Oral Chenodeoxycholate in a Hereditary Anemia Mouse Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Aug 93 ESTIMATED COMPLETION DATE: Indef

PRINCIPAL INVESTIGATOR: CPT George Broughton

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): B Hammaker, T Baker, J Barker

KEY WORDS: Pigmented Gallstones

Study Objective: This study will assess the efficacy of oral chenodeoxycholate (CDCA) in the prevention of pigmented gallstones in a mouse model with hereditary hemolytic anemia.

Technical Approach: Thirty (30) female WBB6F1 +/+ mice will be irradiated and have bone marrow transplants from nb/nb mice (mice with gene that results in hemolytic anemia). The mice will be numbered for identification. Mice will be fed without CDCA for the first two months at WBAMC to become acclimatized and conditioned. They will then be started on CDCA therapy for the next ten months. The drug will be administered at a dose of 10 mg/kg of body weight Monday through Friday. Saturday and Sunday will serve as a drug holiday. Thirty other mice will serve as the placebo control group, and will receive similar husbandry as the study group for the duration of the study. At monthly intervals, liver function panels will be performed on each animal. The animals will be weighed at weekly intervals and the drug dosed accordingly. At the conclusion of the study, the animals will undergo laparotomy for bile collection and gallstone harvest. The bile will be quantitatively and qualitatively analyzed. The anesthetized animals will be euthanized by intracardiac exsanguination. The gallbladder and liver will be removed for histopathologic study.

Progress: This protocal has been terminated because Private Investigator has PCS'd.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/03 STATUS: Ongoing

TITLE: Clinical results of the Biomet Total Knee arthroplasty utilizing the Lone Star extraarticular alignment jig

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Dec 93 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: CPT Jefferson J. Cartwright

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): T Scully, MG Anderson

KEY WORDS: Arthoplasty, Lone Star Jig

Study Objective: To determine if an extraarticular alignment jig allows for more accurate cuts in TKA as evidenced by improvement in radiographic findings and clinical outcome.

Technical Approach: Retrospectively review all TKA patients over the last 2-3 years (approximately 50 patients) who had Biomet implants utilizing the Lone Star Knee jig. Radiographs as well as clinical follow up utilizing the knee society rating score will be performed.

Progress: There have been sixty patients entered in this study and six of them withdrew. There were no noted adverse reactions. To date we have been unable to locate four patients for follow-up studies. Two patients (residing in other states at long distances from El Paso) have declined to return to El Paso for follow-up evaluations. The estimated completion date has been changed from Apr.94 to Jun 95. There has been a change in principal investigator from MAJ Tracey McGee to CPT Jefferson J. Cartwright. This is an outcome study of patients who have undergone total knee orthoplasty procedures at WBAMC. Patients are examined at the point when they exceed two years post-generative follow-up. To this date all follow-up studies (outcome) have been completed on thirty patients. Outcomes on the remaining patients will be evaluated during the next three months.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/27A STATUS: Terminated FY 94

TITLE: Limb Lengthening by Intramedullary Distraction in a Sheep Model; Phase I - Physiologic Feasibility

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 92 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: COL Randolph L. Copeland

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): P Day, P Holzknecht, D Scales, T Baker

KEY WORDS: Bone Lenthening, Intramedullary Rod, Intramedullary Distraction, Limb Lengthening

Study Objective: This testing should demonstrate the feasibility of lengthening a long bone via an intramedullary device in an animal model. The initial phase of the project will be to demonstrate the physiologic potential for adequate new bone to form around an indwelling rod during the process of distraction. Subsequent phases of research would include the practical testing of a prototype indwelling device. Ultimately, a clinical trial in human patients is the goal in the last phases of development. In the process of using the progressive leg lenthening procedure we hope to learn more about the basic physiology of tissue response to stretch. We want to monitor the potential complications, especially infection, which frequently complicates the use of multiple wire external fixators.

Technical Approach: This phase of the research will involve the placement of an intramedullary rod into a long bone of the test animals. The rod initially will be interlocked only at one end. Sufficient room will be allowed at either end of the bone to facilitate application of a standard Ilizarov type fixation device. An osteotomy of the bone will be performed at a location well be outside of the isthmus of the bone so as not to be at the site of minimum diameter and maximum reaming damage to the canal. Lengthening will then be performed after a latency period of 5 days. The distraction will be at a rate of 1 mm per day. The goal of lengthening will be 15% of the measured length of the target bone.

The initial study will involve four test subjects. At the end of distraction, two of the animals in the series will continue with the Ilizarov device. The other two animals will have a subsequent completion of the transverse interlocking screws through the intramedullary rod, followed by removal of the external fixator. At the end of 30 days from cessation of lengthening one of the animals from each group will be euthanized and the limb harvested. The other two animals will be processed at 60 days providing there is evidence on radiographs of substantial new bone formation, otherwise delays of 3 week intervals will be added until at least three cortices demonstrate bridging bone on radiographs.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Amendment (May 93): CPT T Baker has been added as an associate investigator. MAJ Richard Harris has replaced MAJ O'Hair as attending veterinarian. Estimated completion has been extended to January 94.

Progress: This study has been completed. There were 2 subjects entered in the study with no noted adverse reactions.

Abstract: The ability to lengthen a long bone is essential for the treatment of major leg and arm length discrepancies. The current approach to limb lengthening involves the application of an external fixation device to

apply distraction through pins or wires. The procedure is uncomfortable and frequently causes complications. In this project we wanted to determine the effects of an indwelling intramedullary rod during this process of gradual lengthening in hopes of finding an alternative method which would not require devices which impale the soft tissues during the process. Following our protocol two male sheep had surgical lengthening procedures on the tibia. Each had a transverse osteotomy and intramedullary rod placed followed by distraction lengthening by Ilizarov technique. The bones were lengthened 20% of the original length, at which time the rods were distally interlocked and the Ilizarov frames were removed. The first tibia was allowed to heal for 30 days and the second for 60 days at which time the sheep were euthanized. There were some technical difficulties but both animals achieved union of the osteotomy site. Radiographs indicated abundant new bone formation in similar effect as a standard Ilizarov technique. On gross anatomical dissection and microscopic examination there was sufficient neogenerate bone in the lengthened tibia, despite the indwelling intramedullary rod. Histologically, the bone produced significant callous formation consistent with previous reports of distraction lengthening. The observed vascular structures included multiple areas of vessel in-growth in the endosteal region adjacent to the sites of new bone. One of the theoretical disadvantages of lengthening over a intramedullary rod is the possibility of contaminating the rod via pin tract infection. The pins in the subjects of this study had about the usual amount of inflammation and a few had serous drainage which responded to more intense pin site care and in a few cases, soft tissue release was needed. At the time of removal of the fixator, many of the pins were loose as is typical for the technique. Cultures, aerobic and anaerobic, were taken of the medullary canal cavities at both ends of the bones. No organisms were grown from either animal. Obviously a severe pin infection can be a problem, but it would appear that the usual pin drainage is not necessarily a prelude to deep infection. CONCLUSION: Despite the indwelling intramedullary rod, there was insufficient neogenerate bone and vascular in growth to support limb lengthening at a rate of 1 mm/day using the standard Ilizarov technique. The amount of callous formed was consistent with previous reports of the external fixation frame. These conclusions allow us to believe that limb lengthening with an external fixator over a intramedullary rod is a feasible method, without delaying the rate of lengthening of the involved limb. The intramedullary canal appears to be resistant to the introduction of infectious organisms via the transfixing pins although this study is too limited in number to draw a strong conclusion about potential infection. Early removal of the external fixation could avoid some of the potential complications associated with long term external fixation; i.e., pin tract infections and joint contractures. Additionally, a totally implanted intramedullary lengthening device is a theoretical possibility. NOTE: The original protocol called for two additional animal subjects to have the same procedures as the first two but not to have the rods interlocked. This would require a longer term of external fixation. We decided not to pursue this portion of the study because the bones healed so fast with the rods locked and the fixator removed. It would be impossible to show any more rapid consolidation with the rods left unlocked and supported with the fixator. This was designed to be a preliminary feasibility study and has already served that purpose acceptably.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/22 STATUS: Ongoing

TITLE: Iontophoresis: Efficacy of Use in the Treatment of Plantar Fasciitis

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 94 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: 1LT Penny P. Griffith

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Iontophoresis, Plantar Fasciitis

Study Objective: To compare the effects of iontophoresis delivering the dexamethasone corticosteroid to the effects of iontophoresis delivering distilled water when treating plantar fasciitis.

Technical Approach: A randomly assigned double blind study. Patients referred to the physical therapy clinic with the diagnosis of plantar fasciitis will be asked to take part in this study. Subjects participating will undergo standard physical therapy evaluation of range of motion, palpation, ambulatory status, foot biomechanical analysis, and a thorough subjective evaluation. Baseline data will be stored. Each subject will be randomly assigned to one of two treatment groups:

Group 1 (treatment): This group will receive iontophoresis with dexamethasone every other day for 4 sessions.

Group 2 (sham/placebo): This group will receive iontophoresis with distilled water every other day for 4 sessions.

An analysis of variance will be used to detect significant differences between the two groups for each of the tested variables. Significance will be set at 5% level ($p<0.05$).

Progress: The study has been temporarily suspended because the principal investigator is currently in bed rest. The study will resume on January 95 and is expected to be completed by June 95.
There has been a change of principal investigator from MAJ Timothy C. Flynn to Penny P. Griffith. No patients have been enrolled to date.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 90/42A STATUS: Ongoing

TITLE: Fiberoptic Endoscope Cholecystectomy in the Porcine Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 90 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Fiberoptic Endoscope Cholecystectomy

Study Objective: To determine feasibility of conducting cholecystectomies at WBAMC with endoscopic equipment rather than a laparoscope. The experience gained by the professional staff will enable them to develop proficiently to perform such operations in human patients and to determine if additional equipment will be required for the conduct of this procedure.

Technical Approach: No surgical procedures will be conducted without the administration of general anesthesia. Anesthesia will be administered and monitored by Dr. Harris and animal care specialists in the Biological Research Service. The animals' food will be withheld for a period of 18 hours prior to surgery. The pigs' hair will be clipped from the abdomen. The animals will be placed in dorsal recumbency. After the skin is prepped, an insufflation needle will be inserted and the abdomen will be filled with CO2. A trocar will be placed near the umbilicus for introduction of the fiberoptic video endoscope to enable monitoring of the procedure on a video screen. Two to three additional trocars will be placed for introduction of alligator forceps. The cystic duct and artery will be bluntly dissected free, double ligated or clipped, and transected. The gall bladder will be dissected free from the liver bed by sharp, blunt, and electrosurgical techniques. The laser may be used to control hemorrhage and to cut adventitial tissue. Once free from hepatic parenchyma, the gall bladder will be approximated to the body wall and drained with suction. After the bladder is decompressed, it will be pulled through one of the central trocar puncture sites.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: No progress was reported by principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/13A STATUS: Ongoing

TITLE: Resident Training in Laparoscopic and Open Stapling Techniques

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Mar 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

KEY WORDS: Laparoscopic Training

Study Objective: The objectives are to teach the surgical staff and residents proper thoracic and abdominal laparoscopic procedures utilizing stapling instruments and suturing techniques and proper open stapling techniques utilizing the multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers.

Technical Approach: Both video laparoscope and open surgical training techniques will be conducted in the porcine model. The experimental design is such that one or both of the techniques will be conducted on each animal. When both laparoscopic and open techniques are utilized, the laparoscopic techniques will precede the open procedures. The determination of the techniques to be conducted will be done at the time of the training session and will be dependent upon the knowledge and expertise of the residents and staff being trained. After anesthesia induction, the following procedures will be conducted:

(1) Video laparoscopic - Abdominal: cholecystectomy, gastrectomy, small bowel resection, nephrectomy, hysterectomy, splenectomy and partial hepatectomy. Thoracic: esophagectomy, pulmonary resections and vagotomies will be performed utilizing the various stapling instruments and liga clips.

(2) Laparotomy (Open) - Abdominal: A midline incision from the xiphoid process to the pubis will be made. Then a multitude of gastrointestinal staplers, including the TA, GIA, EEA instrumentation, the LDS instrument and the Liga Clip Appliers will be utilized to complete end-to-end, side-to-side colon and small intestinal anastomosis. Additionally, anastomosis will be completed between portions of the small intestine; from the small intestine to stomach and colon; and between the colon and rectum. Transection of the stomach, colon and small intestine will also be performed. Pulmonary: Transection of pulmonary tissue, bronchi, pulmonary arteries and veins will be performed utilizing the various instruments through an intercostal incision.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: No progress was reported by principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 91/15A STATUS: Ongoing

TITLE: Certification Training: Advanced General Surgery Laser Laparoscopic Procedures in the Porcine Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Apr 91 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: LTC Stephen P. Hetz

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

KEY WORDS: Laser Laparoscopy Training

Study Objective: To provide training and certification of General Surgery Surgeons in laser laparoscopic cholecystectomy, hernia repair, and appendectomy. This training will enable them to develop the proficiency required to perform these operative procedures in human patients.

Technical Approach: The animals' food will be withheld for a period of 18 hours prior to surgery. The pigs' hair will be clipped from the abdomen. The animals will be placed in dorsal recumbency. After the skin is prepped, an insufflation needle will be inserted and the abdomen will be filled and maintained with 15 mm Hg pressure of CO2. A trocar/cannula will be placed near the umbilicus for introduction of the video laparoscope which will enable monitoring of the procedure on a video screen. Two to three additional trocars/cannulas will be placed for introduction of laparoscopic graspers, scissors, laser fibers, etc. The cystic duct and artery will be bluntly dissected free, double ligated or clipped, and transected. The gallbladder will be dissected free from the liver bed by sharp, blunt, electrosurgical and laser techniques. Once free from hepatic parenchyma, the gallbladder will be approximated to the body wall, decompressed and pulled through one of the central trocar puncture sites.

Other advanced laparoscopic procedures will include hernia repair and appendectomy. Laparoscopic cannulas will be repositioned as necessary for subsequent procedures to enable visualization and tissue manipulation. Hernia repair- A defect will be created in the internal inguinal ring by sharp and blunt technique. Subsequently, the created hernia will be repaired by laparoscopic suture and stapling techniques. Appendectomy - The distal cecum will be isolated and mobilized. The distal segment will then be resected and closed by laparoscopic suture and stapling techniques. The appendage will be approximated to the body wall with large graspers and removed through a central puncture site.

Training is scheduled for six (6) WBAMC surgeons and ten (10) Sierra surgeons.

Amendment (AUC Approved Apr 91) increased the number of training sessions, animal requirements and resource requirements to accomodate training of 32 physicians.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: No progress was reported by principal investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/18A STATUS: Ongoing

TITLE: Advanced Trauma Life Support Training in the Small Ruminant (Ovine or Caprine Animal Model)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: MAJ Mark S. Kestner

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): W Bowland

KEY WORDS: ATLS Training

Study Objective: This training will enhance the physicians' capabilities of administering advanced trauma life support procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest and abdominal trauma management.

Technical Approach: The Advanced Trauma Life Support (ATLS) training program is designed for physicians who are not primarily responsible for managing the critically injured patient on a day to day basis. The American College of Surgeons (ACS) Committee on Trauma defines the standards that the ATLS course must adhere to. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations. Students then rotate through practical skill stations associated with the lecture content previously presented. The skill stations and animal lab allow the student to observe and practice to proficiency those life-saving skills necessary in the initial management and stabilization of the trauma patient. The animal lab is a one day affair with one instructor and up to five students assigned to each animal.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: There has been a change in the Private Investigator from MAJ Mark S. Kestner to COL Bowland.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/56 STATUS: Ongoing

TITLE: The Use of Marcaine in the Prevention of Post Operative Pain in the Laparoscopic Cholecystectomy Patient

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 93 ESTIMATED COMPLETION DATE: Oct 94

PRINCIPAL INVESTIGATOR: CPT James Sippo

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): SP Hetz, JH Chiles

KEY WORDS: Marcaine Pain Laparoscopic Cholecystectomy

Study Objective: This study will determine if the duration of the procedure, the anesthesia of the diaphragm and the anesthesia of the surgical site reduce post operative pain.

Technical Approach: The study will be a single center, double-blind study which will be prospective in nature.

Progress: Ninety subjects were entered in the study. Fifteen subjects withdrew secondary to conversion to open technique or lost to follow-up. There were no noted adverse reactions. Project is currently ongoing to collect results from 70 patients and is currently under investigation to see if enough data has been collected to form a conclusion to the study.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 93/24 STATUS: Ongoing

TITLE: Pediatric Thyroidectomy: Complications and Strategy

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 93 ESTIMATED COMPLETION DATE: Jan 94

PRINCIPAL INVESTIGATOR: LTC Troy M. Reyna

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S):

KEY WORDS: Thyroidectomy

Study Objective: To determine by retrospective analysis of charts of children undergoing thyroid surgery; what mistakes or acts of omission contributed to the reported complications. Through this study the authors would hope to arrive at a recommended technique for surgical management of thyroid disease in children that optimally treats malignant and benign processes with minimal morbidity.

Technical Approach: A retrospective analysis of all cases of surgically-treated thyroid disease in CONUS will be conducted. The cases will cover the twelve year period 1980-1992. Evaluation will be detailed demographic data, including pathology, type of operation, results, and complications. Analysis will include study of operative reports with regard to documentation and visualization of all parathyroid glands and appropriate-sided recurrent laryngeal nerves and other pertinent anatomical structures.

Progress: Principal investigator is in the process of writing final abstract and manuscript.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/25A STATUS: Ongoing

TITLE: Vascular Changes Associated with Stress Reaction of Bone in the Rat

MONITOR (applicable for projects reviewed semi-annually):

START DATE: May 89 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: COL Thomas J. Scully

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): JM Uhorchak

KEY WORDS: Stress Reaction, Bone

Study Objective: To determine the sequence and character of vascular changes which occur in living bone after it has been subjected to repeated physical stress.

Technical Approach: We will study the character and chronological sequence of vascular changes which occur in rat legs subjected to mechanical stress in the absence of confounding electrical shocks.

a. Thirty anesthetized rats will have their left leg cyclicly mechanically stressed using the techniques of Scully et.al. The tibias will be cyclicly strained to 0.5 mm by repeated application of a 3 point bending load. 10,000 cycles of strain will be applied to the left tibia of each rat at a rate of 10 Hz. The animals will then be recovered from anesthesia and maintained in standard laboratory cages with unrestricted activity, on a standard laboratory diet. Groups of 2 animals will be selected at random on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 12, 15, 18, 24 and 30 days after the initial strain loading.

b. On the date selected the animals will be anesthetized with Nembutal at a dose of 25mg/kg intravenously. The rats will then be heparinized and injected with Xylocaine to prevent vascular thrombosis and to ensure maximum vasodilation. The animals will then be given a lethal dose of Nembutal. After euthanasia the abdomens will be opened through a midline abdominal incision. The aorta and inferior vena cava will be transected and cannulated. Using techniques prescribed in the Microfil product literature the aorta and both lower extremities will be perfused with Microfil at a pressure of 150 mm of mercury. Perfusion will continue until the flow of the Microfil is returned via the inferior vena cava. At that point the animals will be refrigerated to allow overnight curing of the Microfil. As each animal has had only one leg stressed, the contralateral leg will serve as a control. Radiographs will be taken of both lower extremities to delineate the microvascular structure. Microfil is a radio-opaque material. After the radiographs are obtained, tissue clearing will be performed by the following technique: on the first day both tibias will be immersed in a 25% ethanol solution. On the second day 50% ethanol, on the third 75% ethanol, on the fourth day 95% ethanol and on the fifth day a new solution of absolute alcohol. On the sixth day the specimen will be immersed for 24 hours in methylsalicylate. If the tissue is not clear it will be returned to a 95 % ethanol solution and the fine cleaning procedure steps will be repeated. Photographs will then be taken of the vascular tree which will have been filled with colored Microfil. The tibias will then be imbedded and sectioned for standard histologic sectioning.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: All goals of this research project have been successfully completed except for histologic study of sections of the legs (tibias) of rats subjected to cyclic loading stress. The specimens have been maintained in the preserved state. However, all efforts produce thin sections of undecalcified, cleared, rat legs suitable for histologic staining have been only partially successful. Therefore, the specimens have not been processed. Since decalcification

results in some loss of histologic detail, we have been reluctant to use this process prior to histologic staining. However, we have reluctantly decided to accept the slight loss of histologic detail resulting from decalcification and will submit the specimens for routine histologic study after decalcification. This will permit completion of the study. The estimated completion date has changed from June 1994 to June 1995.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/14 STATUS: Terminated FY 94

TITLE: City-Wide Model For Breast Cancer Screening and Data Accumulation in an Ethnically Diverse Border Population

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 94 ESTIMATED COMPLETION DATE: Dec 96

PRINCIPAL INVESTIGATOR: MAJ William C. Sippo

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Algeo, KK Nauschuetz, E Salzstein, LC Mercer, P Graham-Casey, L Gregory, P Golightly, AC Jerigan, V Lutrick, J Widmer

KEY WORDS: Breast Cancer Screening

Study Objective: 1.To screen and collect demographic and medical backgrounds on migrant farm workers, indigent health care recipients, Hispanics, Native Americans, and active duty military and dependents of military personnel;

2.Use the innovative CAREBASE data base to track all patients screened by participating hospitals;

3.Use CAREBASE to develop culturally sensitive educational materials for minority and culturally distinct targeted populations' benefit, including:

(a)promotion of breast self-examinations
(b)increased breast cancer screening
(c)greater access to appropriate health care services

Technical Approach: Female patients from William Beaumont Army Medical Center, Providence Memorial Hospital, Texas Tech, Thomas General Hospital as well as those served by the El Paso Cancer Consortium, will be screened for breast cancer according to current protocols. Each patient screened will be asked to fill out a questionnaire concerning knowledge and attitudes of breast cancer and screening. All data will be recorded and filed according to existing procedures. In addition, all data will be electronically transmitted to the CAREBASE data management system at Texas Tech. After two-years of data accumulation, data will be sorted and analyzed. Recommendations for breast cancer screening derived from Phase I will be submitted during Phase II in another research proposal.

Progress: This study was terminated because funding was not obtained.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/20 STATUS: Ongoing

TITLE: Patient functional outcome, range of motion, and single leg stance differences between two total knee replacement rehabilitation protocols

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 94 ESTIMATED COMPLETION DATE: Jun 95

PRINCIPAL INVESTIGATOR: 1LT Cynthia Weppler

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): N Rossi

KEY WORDS: Total Knee Replacement Rehabilitation

Study Objective: Determine the more effective post-operative rehabilitation of total knee replacement patients.

Technical Approach: All subjects will have pre-operative testing which will include functional assessment score based on results of the Knee Society Clinical Rating System (6, 7) and modified Noyes Knee Questionnaire (11), knee range of motion, timed single leg stance, and gross manual muscle testing of both knees. Subjects will be randomly divided into two groups matched for age, gender, weight, surgeon, prosthesis, preoperative diagnosis and intactness of ACL/PCL ligament. Group 1 will receive post-operative physical therapy according to our present protocol which includes standard strengthening and range of motion exercises, CPM use, ambulation, gait and transfer training; Group 2 will receive ambulation, gait and transfer training only. Interim assessments will be performed at one, three and six month intervals post-operation.This will be a blind study - neither the researchers evaluating the subjects nor the surgeons performing the operations will know the treatment group to which the patient was assigned.Mean, standard deviation, and standard error of the mean will be used to describe each of the variables. One way analysis of variance with repeated measures will be used to detect significant differences for each of the tested variables induced by the two protocols employed. Significance will be chosen at the 5% level ($p<0.05$).

Progress: LT Weppler was unexpectedly reassigned in July 1994. At present there is no one to conduct the study except myself and I do not have anyone to assist me. This study needs to be done, but realistically I will not have support for this until Spring 1995. At that time we may be able to complete it over the following six months. The estimated completion date has changed from June 95 to Oct 95. The principal investigater has changed from 1LT Cynthia Weppler to LTC Noreen M. Rossi.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 89/70A STATUS: Ongoing

TITLE: Tracheal Reconstruction with Synthetic Gore-Tex Grafts in the Rabbit Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Nov 90 ESTIMATED COMPLETION DATE: Jun 94

PRINCIPAL INVESTIGATOR: CPT Charles Whitlow

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): MF Rhodes, M Kestner

KEY WORDS: Tracheal Reconstruction, Tracheal Prosthesis

Study Objective: To identify a tracheal prosthesis material and surgical technique which may be suitable for reconstruction of the human trachea.

Technical Approach: This study will be conducted in two phases. Phase I will be to determine the maximum graft length allowing successful tracheal reconstruction. Phase II will be designed to determine the minimum interval for subcutaneous implantation required to have successful tracheal reconstruction. In both Phase I and II the grafts will be implanted in two stages. The first stage will consist of implantation of the Gore-Tex prosthesis in the subcutaneous tissue with a silastic stent to keep the lumen patient and induce fibrous capsule formation. The animals will then be recovered from anesthesia and monitored for a prescribed period of time. The second stage will consist of harvesting the graft, after an appropriate amount of time is allowed for ingrowth of fibrous tissue, and replacing a segment of trachea with the graft. The animals will then be recovered and observed over a period of three weeks time while receiving prophylactic antibiotics. Initially, two animals will be used to develop the technique and verify suitability of the rabbit as a model. The graft length for these animals will be 1 cm for each rabbit. The graft will remain in the subcutaneous pouch for three weeks prior to the tracheal reconstruction. Three weeks following the tracheal reconstruction, the rabbits will be evaluated to verify patency, infection rates, and degree of re-epithelization in the following manner: The animals will be anesthetized with spontaneous ventilation occurring. Utilizing telescopic bronchoscopy the lumen will be inspected for stenosis. The animal will be euthanatized and the graft cultured and histologically examined for infection and tissue morphology, respectively.
If the outcome of the pilot is successful and the model appears to be appropriate, then the study will proceed as follows:
Phase I: Rabbits will be divided into four groups of six rabbits each:
Group I -3 cm. prothesis length
Group II -4 cm. prothesis length
Group III-5 cm. prothesis length
Group IV -6 cm. prothesis length

The grafts in these animals will be evaluated at intervals of 4 days, 1 week, 3 weeks, 6 weeks, 9 weeks, and 12 weeks. The evaluation will consist of direct laryngoscopy and bronchoscopy with video recording of the procedure and computer analysis of the dynamic change in lumen size with inspiration and expiration.

Criteria for a failed graft will be 30% obstruction of the resting lumen size or a dynamic decrease to 30% of the lumen diameter with respiratory movement. Brush biopsies of the lumenal surface will be taken for bacterial culture and for microscopic evaluation of lumen epithelium. All surgical and bronchoscopy procedures will be conducted only after animals are appropriately anesthetized as stated below. If unable to prevent animal pain or suffering following procedures, the respective rabbits will be euthanatized according to methods stated below. Any animals that die or are euthanatized prior to the termination of the experiment will be necropsied to determine the cause of death, if applicable, and to evaluate the graft sites grossly and microscopically.With the exception of 8 long term animals, all remaining animals will be euthanatized 12 weeks following the tracheal reconstruction.

The grafts will then be excised and examined grossly and microscopically. Two of the remaining animals from each group will be observed for a total of 6 months to determine if any long term complications occur.
Phase II: After determination of the maximum graft length allowing successful reconstruction, the interval between subcutaneous implantation and transfer of the graft for tracheal reconstruction will be evaluated. On this basis the minimal allowable time between subcutaneous transplantation of the Gore-Tex graft and the tracheal reconstruction can be determined. This will be the final phase of the study as planned. Four groups of six animals each will be required. The graft will be implanted as described in Phase I.
Grafts will be harvested as follows:
Group I -one week
Group II -two weeks
Group III-three weeks
Group IV -four weeks

Following harvesting of the PTFE graft and tracheal reconstruction, each group of animals will undergo evaluation as described in Phase I.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: Thirteen rabbits were used in FY93. Improvements in surgical technique have greatly enhanced the success rate for these implants. Problems with stenosis and infection, both of a chronic nature, remain as complications. Principal investigator CPT Canfield has departed WBAMC and is now deployed in Somalia. CPT Charles Whitlow has assumed duties as principal investigator. MAJ Mark Kestner has been added as an associate investigator.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/18A STATUS: Ongoing

TITLE: Thoracoscopic Introduction of Microfibrillar Collagen for Inducing Pleural Symphysis in the Porcine Model (Sus scrofa)

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Feb 94 ESTIMATED COMPLETION DATE: Jan 95

PRINCIPAL INVESTIGATOR: CPT Charles Whitlow

DEPARTMENT: Surgery FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): S Hetz, R Craig

KEY WORDS: Thoracoscopic Pleudesis (Chemical, Talc), Symphysis

Study Objective: To use thoracoscopic techniques for the introduction of microfibrillar collagen in the pleural cavities of pigs to induce pleural symphysis.

Technical Approach: Eighteen adult pigs will be divided into three groups. After undergoing general endotracheal anesthesia (as later described in Part VII, paragraph 9), a 10mm incision will be placed in the lateral chest at the sixth intercostal space. A 10mm thoracoscope will then be introduced and exploration of the pleural cavity performed. A 5mm thoracoport will be placed to facilitate exploration. In six animals (Group A) no further procedure will be performed. A chest tube will be inserted in the thoracoport and residual air removed. The incisions will be closed with absorbable suture and dressed. The animal will be awakened, extubated and returned to the holding area and kept without restrictions. Postoperative analgesia will be under the direct supervision of the staff veterinarian. In six animals (Group B), after exploration is performed mechanical pleurodesis will be performed by abrading the parietal pleura using a gauze sponge introduced through the thoracoport. A third group of six animals (Group C) will undergo thoracoscopic exploration followed by instillation of microfibrillar collagen through the thoracoscope. The removal of residual air, wound closure and postoperative care will be the same in Groups B and C as was described for Group A. At weekly intervals for six weeks one animal from each group will be euthanized. The animals will be necropsied by the investigators. An estimate of gross pleural symphysis will be made and described as a percentage of total pleural surface. Using a tensiometer the lung will be separated from the chest wall at multiple points to judge the degree of pleural symphysis. Finally, microscopic sections of the parietal and visceral pleura will be examined to assess the degree of inflammation and fibrosis. Examiners for all three methods of assessing degree of symphysis will be blinded with regards to the group from which each animal came.

Progress: To date 15 pigs have been pleurodesed and euthanized. Microscopic and gross examination has been performed on those animals. Three more animals will be pleurodesed on 5 Oct 94 and euthanized within the ensuing 6 weeks. Tensiometry will be performed on all specimens following completion of pleurodesis on all 18 animals. The estimated completion date has changed from Aug 94 to Jan 95.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 92/11A STATUS: Ongoing

TITLE: Emergency Life Support Training for Combat Medics in the Small Ruminant (Ovine or Caprine) Animal Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Jan 92 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: 2LT Hector Vega

DEPARTMENT: ADA FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): J Walls

KEY WORDS: Emergency Life Support

Study Objective: This training will enhance the combat medical aidman's (Medic's) capabilities of administering emergency lifesaving procedures to patients with emergency medical conditions which require establishment of airways, venous access, and chest trauma management.

Technical Approach: The emergency life support training program is designed for medics who are responsible for providing first to third echelon care to the critically injured patient (echelon 1- self & buddy aid; echelon 2- combat lifesaver; echelon 3- medical specialist). Procedures taught will be according to the American College of Surgeons (ACS) Committee's Advanced Trauma Life Support Course. Initial assessment and management of specific types of injuries are presented to the student through lecture and slide presentations and a written examination. Students who successfully complete lecture and examination requirements, then rotate through animal laboratories associated with the lecture content previously presented. The animal laboratory allows the student to observe and practice to proficiency those life-saving skills necessary in the initial management and stabilization of the trauma patient. The animal laboratory is approximately 2-3 hours per cycle. Each animal station will consist of one instructor and no more than four to five students.

NOTE: All procedures producing pain or discomfort to these animals have been described in full and such pain and discomfort will be effectively minimized with tranquilizers, and/or anesthetics as required under Public Laws 89-544, 91-579, 94-279, and 99-198 (The Animal Welfare Act and Amendments). All exceptions are described in the protocol in item 5.b. (Animal Procedures).

Progress: A total of 18 combat medics and physician's assistants completed the ATLS training program under this protocol in FY94. After action reports and critiques indicated that this training was very well received and judged as extremely valuable in familiarizing emergency medical personnel in actual hands-on life saving techniques.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 88/52A STATUS: Ongoing

TITLE: Combat Trauma Life Support Procedure in the Sheep Model

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 88 ESTIMATED COMPLETION DATE: Indefinite

PRINCIPAL INVESTIGATOR: 1LT J. Walls

DEPARTMENT: 3ACR FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): A Montes

KEY WORDS: Life support, Combat trauma

Study Objective: To train Physicians Assistants and Line Medics who are not dealing with major trauma on a day-to-day basis, but may be called upon to perform this function in a combat environment. The sheep model will simulate human trauma.

Technical Approach: Animal procedures include:

1. Cricothyroidotomy
2. Venous Cutdown
3. Intubation
4. Chest Trauma Management
    a. Needle decompression
    b. Tube thoracostomy

ATLS training manuals will be used for each training procedure.

Progress: A total of 34 combat medics and physician's assistants completed the ATLS training program under this protocol in FY94. After action reports and critiques indicated that this training was very well received and judged as extremely valuable in familiarizing emergency medical personnel in actual hands-on life saving techniques.

DETAIL SUMMARY SHEET

DATE: 1 October 1994 PROTOCOL #: 94/44A STATUS: Ongoing

TITLE: Gene Amplification as a Tool for the Rapid and Direct Diagnosis of Mycobacterium bovis and Mycobacterium tuberculosis in Dairy Cattle

MONITOR (applicable for projects reviewed semi-annually):

START DATE: Oct 94 ESTIMATED COMPLETION DATE: Dec 94

PRINCIPAL INVESTIGATOR: John B. Westover, DVM

DEPARTMENT: USDA FACILITY: William Beaumont Army Medical Center

ASSOCIATE INVESTIGATOR(S): WF Nauschuetz, S Mahlen, SD Pillai

KEY WORDS: Mycobacterium Tuberculosis, Mycobacterium Tuberculosis

Study Objective: The purpose of this study will be to demonstrate the presence of M. bovis and M. tuberculosis in nasal swabs and milk samples from dairy cattle, as well as sputum samples from humans. A rapid diagnostic test for mammalian Mycobacterium species utilizing quantitative PCR techniques is to be evaluated as the primary objective for this project.

The study proposes to introduce the Polymerase Chain Reaction (PCR) technology for the identification of M. tuberculosis and M. bovis. Veterinary Services, APHIS, USDA will participate in a joint investigation with the Department of Clinical Investigation, WBAMC an and the El Paso City/County Health District to investigate the sensitivity of PCR compared to routine TB culture and susceptibilities for the detection of M. tuberculosis and M. bovis. The principal investigators are working towards an agreement with management from TB quarantined dairies in Texas and dairies at risk for the infection in Chihuahua, Mexico to acquire clinical specimens for PCR and TB culture evaluation.

The data derived from this study can be used to evaluate and establish the El Paso-Juarez region as a high-risk area for bovine and human forms of tuberculosis, and provide some insight on the dynamics of M. tuberculosis and M. bovis in human and livestock populations. The implementation of the PCR amplification techniques for the rapid detection of TB is to be evaluated for field application in an endemic region.

Technical Approach: EXPERIMENTAL DESIGN: Amplification of the IS6110 sequence in M. bovis and M. tuberculosis will be optimized with primers IS1 (5'- CCTCGCAG CGTAGGCGTCGG-3') and IS2 (5'- CTCGTCCAGCGCCGCTTCGG-3'). These primers will be used to amplify DNA from an ATCC strain of M. tuberculosis (Eisenach, 1991). Amplifications will be run on the Perkin-Elmer 9600. The amplification cycle will be 95oC, 65oC and 72oC. Length, and number, of cycles will be determined during optimization.

The presence of amplified mycobacterial DNA will be detected by electrochemiluminescence using the automated Perkin-Elmer QPCR 5000. Amplified DNA will be hybridized to the specific detection probe (5'- CTGCCCAGGTCGACACAT-3').

DESCRIPTION OF PROCEDURES, TECHNIQUES, OR TESTS: Specimen material, in the form of nasal swabs and milk samples, will be collected from cattle maintained at local commercial dairies. Microbial determination for M. bovis and M. tuberculosis will consist of standard PCR amplification procedures conducted within the Department of Clinical Investigations, with histopathologic and bacterial culture techniques performed within the Department of Pathology. No surgical procedures or invasive techniques are to be utilized as a result of this protocol.

Progress: This study has just started therefore no progress has been reported.

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